SOME SYNTHETICAL EXPERIMENTS ON ORGANIC BASES.

T H E S I S

presented by

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THE REDUCTION OF NITRO-COMPOUNDS BY AROMATIC KETOLS. PART I. SOME *p*-AZOXY-COMPOUNDS.

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CCLXXV.—*The Reduction of Nitro-compounds by Aromatic Ketols. Part I. Some* p-*Azoxy-compounds.*

By Hugh Bryan Nisbet.

That benzoin and its analogues may reduce Fehling's solution has been known for a long time, but the possibility of reducing nitro-groups by means of these agents has not hitherto been investigated. It has now been found that benzoin, anisoin, and furoin, in hot alcoholic solution in the presence of a trace of sodium methoxide or ethoxide, may be successfully used for the reduction of nitro-groups to azoxy-groups :

$$2R{\cdot}NO_2 + 3R{\cdot}CH(OH){\cdot}COR = R_2N_2O + 3R{\cdot}CO{\cdot}COR + 3H_2O.$$

The reduction is particularly successful in the case of *p*-nitro-compounds such as the *p*-nitrobenzylideneanilines, *p*-nitrobenzonitrile, the *p*-nitrocinnamic esters, and the *p*-nitrostilbenes, since the azoxy-compounds formed are, in general, sparingly soluble substances and may be readily separated from the 1 : 2-diketone to which the ketol is oxidised in the course of the reaction. The reduction proceeds very quickly, in some cases with ebullition of the solvent, and in a very short time the *p*-azoxy-compounds separate from solution. The 1 : 2-diketone may be recovered in each case from the mother-liquor.

With benzoin as reducing agent, 60—70% yields of *p*-azoxybenzylideneanilines can be obtained from the corresponding *p*-nitrobenzylideneanilines. *p*-Azoxybenzylideneaniline so obtained is identical with that obtained by reducing *p*-nitrobenzylideneaniline with alkali sulphides (*Chem. Zentr.*, 1900, ii, 612) or with alcoholic potash (Alway, *Ber.*, 1902, **35**, 2436), by treating *p*-nitrobenzyl chloride with caustic potash (Alway, *loc. cit.*), or by condensing *p*-azoxybenzaldehyde with aniline (Alway, *Amer. Chem. J.*, 1902, **28**, 43). *p*-Azoxybenzylidene-*p*-toluidine prepared by this method is identical with the compound prepared by reducing *p*-nitrobenzylidene-*p*-toluidine with alkali sulphides (*Chem. Zentr.*, 1900, ii, 612) or by the condensation of *p*-azoxybenzaldehyde with *p*-toluidine (Alway, *Ber.*, 1902, **35**, 2437). *p*-Nitrobenzylidene-*p*-aminoacetophenone is reduced by benzoin to *p*-azoxybenzylidene-*p*-aminoacetophenone.

Japp and Miller (J., 1893, **63**, 474) showed that benzoin and benzonitrile in the presence of concentrated sulphuric acid condense to form triphenyloxazole ; but *p*-nitrobenzonitrile is reduced by benzoin to *p*-azoxybenzonitrile.

By this method of reduction the esters of *p*-azoxycinnamic acid can be prepared directly from the esters of *p*-nitrocinnamic acid,

and the azoxy-acid can be obtained by hydrolysis. The yields of the reduction products are good, usually 70%, and the reaction proceeds very quickly, whereas the reduction of the nitro-acid electrolytically (Marie, *Compt. rend.*, 1905, **140**, 1248) or by sodium arsenite (Vorländer, *Ber.*, 1906, **39**, 806) and the formation of the esters of the azoxy-acid through the silver salt (Vorländer, *loc. cit.*) are all tedious methods.

p-Nitrostilbenes also are easily reduced by this method to *p*-azoxystilbenes, which may be obtained in excellent yield. The table gives the *p*-azoxystilbenes prepared by this method, the approximate yield, usually the average of two experiments, and the molecular weights of those compounds which are sufficiently soluble in 2 : 4-dinitrotoluene to allow of the determination by the cryoscopic method in that solvent (Auwers, *Z. physikal. Chem.*, 1899, **30**, 310).

Azoxy-compounds.	Yield.	*M*, found.	*M*, calc.
p-Azoxystilbene	70%	396	402
p-Azoxy-2-nitrostilbene	70%	487	492
p-Azoxy-2 : 3′-dinitrostilbene	45%	—	—
p-Azoxy-2 : 6-dinitrostilbene	Small	—	—
p-Azoxy-2-nitro-4′-methoxystilbene	70%	512	552
p-Azoxy-2-nitro-3′ : 4′-methylenedioxystilbene	65%	586	580
p-Azoxy-2 : 6-dinitro-4′-methoxystilbene	45%	—	—
p-Azoxy-2-nitro-4′-dimethylaminostilbene	42%	—	—

Anisoin and furoin were substituted for benzoin in the reduction of 2 : 4-dinitrostilbene and gave approximately the same yield of the same azoxy-compound. The mother-liquors yielded anisil and furil, respectively. In all the reductions in which benzoin was used, benzil was recovered from the mother-liquors.

Experimental.

Preparation of Nitrostilbenes.—A modification of Bishop and Brady's method (J., 1922, **121**, 2367) was used. A solution of the polynitrotoluene and the aromatic aldehyde in molecular proportion and 1 c.c. of piperidine in a small quantity of benzene is boiled under reflux until the reaction is complete, the time varying from 1 to 6 hours. The benzene is then allowed to evaporate and the crystalline mass is washed with benzene–light petroleum and recrystallised from glacial acetic acid. 2 : 4-Dinitro-4′-methoxystilbene, 75% yield, m. p. 163° (compare Pfeiffer, *Annalen*, 1916, **411**, 91). 2 : 4 : 3′-Trinitrostilbene, 50% yield, m. p. 182—183° (compare Pfeiffer, *loc. cit.*). 2 : 4 : 4′-*Trinitrostilbene*, from 2 : 4-dinitrotoluene (9 g.) and *p*-nitrobenzaldehyde (7·5 g.). Yield, 12 g. Dark orange needles, m. p. 234—235° (Found : C, 53·9; H, 3·0. $C_{14}H_9O_6N_3$ requires C, 53·3; H, 2·9%). 2 : 4-*Dinitro*-3′ : 4′-*methylenedioxystilbene* from 2 : 4-dinitrotoluene (9 g.) and piperonal

(7·5 g.). Yield, 12 g. Orange-red, squat crystals, m. p. 178—180° (Found: C, 56·9; H, 3·3. $C_{15}H_{10}O_6N_2$ requires C, 57·3; H, 3·2%). 2 : 4 : 6-*Trinitro-4'-methoxystilbene*, from 2 : 4 : 6-trinitrotoluene (11 g.) and anisaldehyde (7 g.). Yield, 9·3 g. Brown needles, m. p. 167—168° (Found: C, 51·8; H, 3·3. $C_{15}H_{11}O_7N_3$ requires C, 52·2; H, 3·2%). 2 : 4-*Dinitro-4'-dimethylaminostilbene*, from 2 : 4-dinitrotoluene (9 g.) and *p*-dimethylaminobenzaldehyde (7 g.). Yield, 11 g. Small, black, lustrous plates, m. p. 181° (Found: N, 12·8. $C_{16}H_{15}O_4N_3$ requires N, 12·8%). The base forms a *chloroplatinate*, yellowish-brown needles, m. p. 211° [Found: Pt, 18·8. $(C_{16}H_{15}O_4N_3)_2,H_2PtCl_6$ requires Pt, 18·9%].

Preparation of Azoxy-compounds. General Method and Remarks.—The nitro-compound is dissolved in the smallest possible quantity of boiling alcohol, sufficient ketol for the reduction of somewhat less than the whole of the nitro-compound is added, and then a few drops of 6% alcoholic sodium methoxide or ethoxide. The solution goes dark, but soon begins to clear and a yellow or an orange precipitate settles out. After cooling a little, this is collected, dried, and recrystallised from xylene. The azoxy-compounds so obtained are, in general, yellow or bronze-yellow, and are very slightly soluble in the common solvents, slightly soluble in boiling xylene, and more soluble in boiling pyridine. If too much reducing agent be added, the reduction products are sometimes red, probably due to the formation of traces of azo-compounds.

The constitutions of the *p*-azoxystilbenes follow from the analytical figures and the molecular-weight determinations, and from their analogy to the other compounds described in this paper. That it is the *p*-nitro-group which is reduced in stilbenes containing more than one nitro-group may be safely assumed, since it has been proved already that other alkaline reducing agents, *e.g.*, ammonium sulphide, attack the *p*-nitro-group first (Thiele and Escales, *Ber.*, 1901, **34**, 2846). The insolubility of the *p*-azoxystilbenes which have been prepared so far by this method has rendered the examination of further reduction products impossible.

p-*Azoxybenzylideneaniline*, $(C_6H_5{\cdot}N{:}CH{\cdot}C_6H_4)_2N_2O$. *p*-Nitrobenzylideneaniline (8 g.) and benzoin (8 g.) gave an almost immediate separation of yellow flakes which, recrystallised from xylene, sintered at 185° and melted and decomposed at 226°. Yield, 5 g. (Found: C, 77·2; H, 5·2; N, 13·8. Calc.: C, 77·2; H, 4·95; N, 13·8%). The compound was completely identified by treating it with 27% nitric acid; *p*-azoxybenzaldehyde, m. p. 190°, and aniline were obtained (compare Alway, *Amer. Chem. J.*, 1902, **28**, 43). The *p*-azoxybenzaldehyde recondensed with aniline to give *p*-azoxybenzylideneaniline which, when mixed with the product

obtained by using benzoin as reducing agent, did not alter its melting point.

p-*Azoxybenzylidene*-p-*toluidine*, $(C_7H_7N{:}CH{\cdot}C_6H_4)_2N_2O$. *p*-Nitrobenzylidene-*p*-toluidine (2·5 g.) and benzoin (2·1 g.) gave an immediate separation of yellow flakes, which were recrystallised from boiling xylene. M. p. 217° (decomp.; sintering at 189—190°). Yield, 1·7 g. (Found: C, 77·9; H, 5·9; N, 12·5. Calc.: C, 77·7; H, 5·55; N, 12·9%).

p-*Azoxybenzylidene*-p-*aminoacetophenone*,

$$(CH_3{\cdot}CO{\cdot}C_6H_4{\cdot}N{:}CH{\cdot}C_6H_4)_2N_2O.$$

p-Nitrobenzylidene-*p*-aminoacetophenone (2·7 g.) and benzoin (2·1 g.) gave an immediate separation of yellow flakes. Recrystallised from xylene, the substance sintered at 187° and melted and decomposed at 217°. Yield, 1·8 g. (Found: C, 73·4; H, 5·15; N, 11·3; *M*, cryoscopic in 2 : 4-dinitrotoluene, 486. $C_{30}H_{24}O_3N_4$ requires C, 73·8; H, 4·9; N, 11·6%; *M*, 488).

p-*Azoxybenzonitrile*.—*p*-Nitrobenzonitrile was prepared by Sandmeyer's method (*Ber.*, 1885, **18**, 1492), but was isolated, not by sublimation, but by extracting the cuprocyanide reaction mixture several times with much boiling water; it was deposited in flakes on cooling and recrystallised from alcohol (yield, 8·2 g. from 13·8 g. of *p*-nitroaniline).

p-Nitrobenzonitrile (6 g.) and benzoin (8·5 g.) were dissolved in 100 c.c. of alcohol, and a few drops of 6% alcoholic sodium ethoxide added. p-*Azoxybenzonitrile* soon began to separate and after cooling it was collected and recrystallised from boiling toluene (yield, 5 g.); m. p. 221° (Found: C, 67·9; H, 3·5; N, 22·5; *M*, cryoscopic in 2 : 4-dinitrotoluene, 247. $C_{14}H_8ON_4$ requires C, 67·7; H, 3·2; N, 22·5%; *M*, 248).

Esters of p-*azoxycinnamic acid*. Ethyl *p*-nitrocinnamate (3 g.) and benzoin (3 g.) gave ethyl *p*-azoxycinnamate (2·1 g.), which crystallised from xylene in yellow, flocculent needles, m. p. 240°, sintering at 140° (Found: C, 67·1; H, 5·5; N, 7·1. Calc.: C, 67·1; H, 5·5; N, 7·2%).

Methyl *p*-nitrocinnamate (2 g.) and benzoin (2 g.) gave 1·4 g. of methyl *p*-azoxycinnamate, which crystallised from xylene in yellow, flocculent needles, m. p. 246°, sintering at 220° (Found: C, 65·8; H, 4·8; N, 7·35. Calc.: C, 65·6; H, 4·9; N, 7·6%).

p-Azoxycinnamic acid was obtained, by hydrolysis of either of the esters, as a yellow, amorphous solid insoluble in the common organic solvents but soluble in alkali; it decomposed at a high temperature (Found: C, 64·2; H, 4·3; N, 7·8. Calc.: C, 63·9; H, 4·1; N, 8·2%).

p-*Azoxystilbene*, $(C_6H_5{\cdot}CH{:}CH{\cdot}C_6H_4)_2N_2O$. 4-Nitrostilbene (1·7 g.)

and benzoin (1·6 g.), treated according to the general method, gave a green solution which in a short time turned yellow and deposited a yellow, flocculent precipitate. This, after recrystallisation from xylene, sintered at 259° and melted and decomposed at 271—272° (Found: C, 83·2; H, 5·6; N, 6·9; *M*, 396. $C_{28}H_{22}ON_2$ requires C, 83·5; H, 5·5; N, 6·9%; *M*, 402).

p-*Azoxy*-2-*nitrostilbene*. Reduction of 2 : 4-dinitrostilbene (Bishop and Brady, J., 1922, **121**, 2367) (2·6 g.) with benzoin (2·1 g.), anisoin (2·6 g.), or furoin (1·9 g.) gave 1·8 g., 1·75 g., or 1·8 g., respectively, of the p-*azoxy*-compound, which crystallised from xylene in orange plates, m. p. 208—210° (Found: C, 68·2; H, 4·2; N, 11·4; *M*, 487. $C_{28}H_{20}O_5N_4$ requires C, 68·3; H, 4·1; N, 11·3%; *M*, 492). Anisil, m. p. 133°, and furil, m. p. 162°, were obtained from their respective mother-liquors.

p-*Azoxy*-2 : 3′-*dinitrostilbene*. 2 : 4 : 3′-Trinitrostilbene (1·6 g.) and benzoin (1·1 g.) gave 0·75 g. of the reduction compound, which crystallised from xylene in yellow flakes, m. p. 212° (Found: C, 58·1; H, 3·4; N, 14·4. $C_{28}H_{18}O_9N_6$ requires C, 57·7; H, 3·1; N, 14·4%).

p-*Azoxy*-2 : 4′-*dinitrostilbene*. Only traces of this reduction compound could be isolated, since it was difficult to find a suitable solvent for the nitrostilbene.

p-*Azoxy*-2 : 6-*dinitrostilbene*. 2 : 4 : 6-Trinitrostilbene (Bishop and Brady, *loc. cit.*) (3·2 g.) and benzoin (2·1 g.) gave on standing over-night a small yield of a solid which, recrystallised from glacial acetic acid, had m. p. 270° (Found: N, 14·6. $C_{28}H_{18}O_9N_6$ requires N, 14·4%).

p-*Azoxy*-2-*nitro*-4′-*methoxystilbene*. 2 : 4-Dinitro-4′-methoxystilbene (3·1 g.) and benzoin (2·1 g.) gave 2·2 g. of the *azoxy*-compound, which is only slightly soluble in boiling xylene and is an orange-red, microcrystalline powder, m. p. 208° (Found: C, 65·8, 64·75, 64·75; H, 4·7, 4·5, 4·6; N, 10·0; *M*, 512. $C_{30}H_{24}O_7N_4$ requires C, 65·2; H, 4·3; N, 10·1%; *M*, 552).

p-*Azoxy*-2-*nitro*-3′ : 4′-*methylenedioxystilbene*. 2 : 4-Dinitro-3′ : 4′-methylenedioxystilbene (2·8 g.) and benzoin (2·1 g.) gave 1·7 g. of the p-*azoxy*-compound which, recrystallised from xylene, formed a red, microcrystalline solid, m. p. 230° (Found: C, 62·1; H, 4·0; N, 9·4; *M*, 586. $C_{30}H_{20}O_9N_4$ requires C, 62·0; H, 3·5; N, 9·6%; *M*, 580).

p-*Azoxy*-2 : 6-*dinitro*-4′-*methoxystilbene*. 2 : 4 : 6-Trinitro-4′-methoxystilbene (2·8 g.) and benzoin (2·1 g.) gave 1·25 g. of the p-*azoxy*-compound, which forms bronze plates from xylene. It changes colour at 252° and melts with decomposition at 297° (Found: C, 55·6; H, 3·6; N, 13·2. $C_{30}H_{22}O_{11}N_6$ requires C, 55·9; H, 3·4; N, 13·06%).

p-*Azoxy*-2-*nitro*-4′-*dimethylaminostilbene*. 2 : 4-Dinitro-4′-dimethylaminostilbene (1·5 g.) and benzoin (1 g.) gave black, flaky crystals of the p-*azoxy*-compound which were washed with hot alcohol. The compound is so slightly soluble in boiling xylene that it cannot be recrystallised from that solvent. The substance without further purification remained unchanged at 305° (Found: N, 14·3. $C_{32}H_{30}O_5N_6$ requires N, 14·5%). The compound is soluble in hot concentrated hydrochloric acid, but the hydrochloride is readily hydrolysed on addition of water. Two attempts to prepare a chloroplatinate failed owing to the almost colloidal nature of the hydrochloric acid solution.

The mother-liquors from each of the above reductions in which benzoin was used yielded benzil, m. p. 95°, on standing or when poured into water and the needles so obtained were recrystallised from alcohol. The compound was identified by its characteristic reaction with alcoholic potash and by its oxidation to benzoic acid, m. p. 122°, by means of alkaline permanganate.

The investigation is being continued with a view to establishing the generality of this method of reducing nitro- to azoxy-groups and determining its value as a method of preparing azoxy-compounds.

In concluding this part of the work, the author desires to thank Professor A. Archibald Boon for his kind interest and for providing the facilities which have rendered this research possible.

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CCCCX.—*The Reduction of Nitro-compounds by Aromatic Ketols. Part II. Some* o-, m-, *and* p-*Azoxy-compounds.*

By Hugh Bryan Nisbet.

In extending the work already done (Part I, J., 1927, 2081), it has been proved that benzoin and its homologues in hot alcoholic solution under the influence of a trace of sodium ethoxide reduce nitro-groups to azoxy-groups no matter what position these occupy in the benzene ring. Whilst the reaction, as a method of preparing azoxy-compounds, still continues to be particularly successful in the case of para-compounds and more particularly in the case of para-compounds containing a carbon-to-carbon or a carbon-to-nitrogen double bond, yields of the order 50—87% being obtained, it is not so successful in the case of *o*- and *m*-compounds, the yields dropping to the order of 6—50%.

The isolation of the azoxy-compound from the accompanying diketone is the main difficulty, for only methods of fractional crystallisation can be resorted to because azoxy-compounds readily decompose when distilled, even in a vacuum, especially when in admixture with other compounds. *p*-Azoxy-compounds are usually much less soluble in common solvents than benzil and can, in general, be easily separated even in alcoholic solution. *o*- and *m*-Azoxy-compounds, however, are as soluble as or more soluble than the diketone, which is often the first product of the reaction, whilst the azoxy-compound must be isolated from the mother-liquors. In many cases it has been found impossible to isolate the azoxy-compound; but in every case examined it has been possible to separate the diketone and thus prove that the nitro-group has oxidised the ketol and has at the same time suffered reduction. This reaction is utilised in a new preparation of anisil and furil by oxidation of the corresponding ketol with nitrobenzene.

o-, *m*-, and *p*-Azoxy-compounds have been prepared from *o*-, *m*-,

and *p*-nitrobenzylideneacetophenone, 2-*o*-, 2-*m*-, and 2-*p*-nitrostyryl-3-methylchromone, and *o*-, *m*-, and *p*-nitrobenzylidene-*p*-bromoaniline. *p*-Azoxybenzylidene-*p*-toluidine has already been described (J., 1927, 2084); the m-*azoxy*-compound has now been prepared, but the *o*-azoxy-compound could not be isolated. Ethyl *p*-nitrobenzoate is reduced to ethyl *p*-azoxybenzoate, but the isolation of the esters of *m*-and *o*-azoxybenzoic acids could not be accomplished. The preparation of *o*- and *m*-azoxybenzonitrile, of azoxybenzene, and of α-azoxynaphthalene (compare Cumming and Steele, J., 1923, **123**, 2466) failed. In each case, however, benzil was separated.

EXPERIMENTAL.

Preparation of 2-Nitrostyryl-3-methylchromones.—2 : 3-Dimethylchromone was condensed with the corresponding nitrobenzaldehyde by Heilbron, Barnes, and Morton's method (J., 1923, **123**, 2565).

2-o-*Nitrostyryl*-3-*methylchromone*, $C_6H_4<\begin{matrix}CO\cdot CMe\\ O—C\cdot CH{:}CH\cdot C_6H_4\cdot NO_2\end{matrix}$. 2 : 3-Dimethylchromone (2·8 g.) and *o*-nitrobenzaldehyde (2·2 g.) gave 1·6 g. of a solid which recrystallised from glacial acetic acid in yellow needles, m. p. 161° (Found: N, 4·5. $C_{18}H_{13}O_4N$ requires N, 4·55%).

2-m-*Nitrostyryl*-3-*methylchromone*. The chromone (3·4 g.) and *m*-nitrobenzaldehyde (3 g.) gave a solid which recrystallised from acetone in greenish-yellow needles (3 g.), m. p. 212° (Found: N, 4·55%).

2-p-*Nitrostyryl*-3-*methylchromone*, similarly prepared from *p*-nitrobenzaldehyde (3 g.), crystallised from glacial acetic acid in orange-yellow needles (2·8 g.), m. p. 238° (Found: N, 4·5%).

Preparation of Azoxy-compounds. General Method and Remarks.—The general method described in Part I (*loc. cit.*) was again employed. In those cases in which the azoxy-compound did not separate immediately or on standing for some time, some of the alcohol was distilled off and the reaction mixture was again kept until needles of benzil crystallised. These were filtered off and the mother-liquor was poured into water. The solid which separated (a mixture of benzil and azoxy-compound) was then dried and dissolved in the minimum quantity of benzene or xylene, and the azoxy-compound precipitated by addition of light petroleum.

A modification of the process, with benzene as a solvent and piperidine as an activator, was used in the preparation of 2-nitro-4-azoxytoluene.

p-*Azoxybenzylideneacetophenone*, $(C_6H_5\cdot CO\cdot CH{:}CH\cdot C_6H_4)_2N_2O$. *p*-Nitrobenzylideneacetophenone (4·2 g.) and benzoin (5·4 g.) gave 3·5 g. (87% of the theoretical yield) of the *p*-azoxy-compound,

which recrystallised from xylene in yellow flakes, m. p. 211—213° (compare Vorländer, *Ber.*, 1906, **39**, 810) (Found : N, 5·8. Calc. : N, 6·1%).

m-*Azoxybenzylideneacetophenone*. *m*-Nitrobenzylideneacetophenone (4·8 g.) and benzoin (6·5 g.) gave an oily solid which crystallised after some time. Recrystallised from dilute acetone and finally purified by dissolution in hot xylene and precipitation with light petroleum, it gave a brown, microcrystalline solid, m. p. 156—157°. Yield, 0·75 g. (6%) (Found : N, 6·1. $C_{30}H_{22}O_3N_2$ requires N, 6·1%).

o-*Azoxybenzylideneacetophenone*. *o*-Nitrobenzylideneacetophenone (4·6 g.) and benzoin (6·36 g.) gave benzil (4·5 g.) as a first product, and the mother-liquor, poured into water, gave a brown solid which crystallised from benzene and light petroleum in brown flakes, m. p. 141—142° after softening at 135°. Yield, 1·2 g. (11%) (Found : N, 6·2%).

2-p-*Azoxystyryl*-3-*methylchromone*. 2-*p*-Nitrostyryl-3-methylchromone (1·5 g.) and benzoin (1·1 g.) gave 0·6 g. (43%) of the p-*azoxy*-compound, which recrystallised from xylene in orange-yellow flakes, m. p. 289° (Found : N, 5·0. $C_{36}H_{26}O_5N_2$ requires N, 4·9%).

2-m-*Azoxystyryl*-3-*methylchromone* (0·75 g.; 62%), prepared from 2-*m*-nitrostyryl-3-methylchromone (1·3 g.) and benzoin (1·2 g.), separated from xylene as a yellowish-white, microcrystalline solid, m. p. 275·5° (Found : N, 5·0%).

2-o-*Azoxystyryl*-3-*methylchromone* (0·2 g.; 15%), obtained from 2-*o*-nitrostyryl-3-methylchromone (1·5 g.) and benzoin (1·3 g.), formed greenish-yellow needles, m. p. 202° (Found : N, 4·8%).

p-*Azoxybenzylidene*-p-*bromoaniline*, $(C_6H_4Br\cdot N{:}CH\cdot C_6H_4)_2N_2O$, (1 g.; 55%), prepared from *p*-nitrobenzylidene-*p*-bromoaniline (2 g.) and benzoin (2 g.), recrystallised from glacial acetic acid in yellowish-red plates, m. p. 218° (Found : N, 10·15. $C_{26}H_{18}ON_4Br_2$ requires N, 10·0%).

m-*Azoxybenzylidene*-p-*bromoaniline*. m-*Nitrobenzylidene*-p-*bromoaniline* was prepared by heating *m*-nitrobenzaldehyde and *p*-bromoaniline together until no more water was given off. It crystallised from alcohol in long, yellow needles, m. p. 84° (Found : N, 9·4. $C_{13}H_9O_2N_2Br$ requires N, 9·2%).

m-Nitrobenzylidene-*p*-bromoaniline (4 g.) and benzoin (4 g.) gave on standing for some time 0·7 g. (19%) of the m-*azoxy*-compound, which separated from benzene and light petroleum as a yellow, microcrystalline solid, m. p. 120° (Found : N, 10·15. $C_{26}H_{18}ON_4Br_2$ requires N, 10·0%).

o-*Azoxybenzylidene*-p-*bromoaniline* (0·5 g.; 27%), obtained from

o-nitrobenzylidene-*p*-bromoaniline (2 g.) and benzoin (2 g.) after standing for 2 days, crystallised from xylene and light petroleum in yellow needles, m. p. 299° (Found : N, 10·3%).

m-*Azoxybenzylidene*-p-*toluidine* (2 g.; 46%), obtained from *m*-nitrobenzylidene-*p*-toluidine (4·8 g.) and benzoin (5 g.) after standing for some time, was recrystallised, first from glacial acetic acid and then from benzene and light petroleum; it formed pale yellow needles, m. p. 150° after softening at 135° (Found : N, 13·0. $C_{28}H_{24}ON_4$ requires N, 13·0%).

Ethyl *p*-azoxybenzoate (2·75 g.; 78%), prepared from ethyl *p*-nitrobenzoate (4 g.) and benzoin (6·5 g.), crystallised from glacial acetic acid in salmon-pink needles, m. p. 117° (compare Meyer and Dahlem, *Annalen*, 1903, **326**, 334) (Found : N, 8·3. Calc. : N, 8·2%).

2-*Nitro*-3-*azoxytoluene*. A solution of 2 : 4-dinitrotoluene (5 g.) and benzoin (10 g.) in 15 c.c. of benzene containing 2 c.c. of piperidine was boiled under reflux for 6 hours. The solvent was then allowed to evaporate almost to dryness. The solid which separated, after being washed with a little cold benzene and recrystallised from glacial acetic acid and from benzene–light petroleum, formed yellowish-white needles, m. p. 164° (compare Brand and Zöller, *Ber.*, 1907, **40**, 3329). Yield, 1 g. (23%) (Found : N, 17·6. Calc. : N, 17·7%).

Preparation of Anisil and Furil.—Although azoxybenzene could not be isolated in the reduction of nitrobenzene by means of benzoin, anisoin, or furoin, by using excess of the oxidising agent it was found possible to utilise the reaction as a method of preparing anisil and furil in 80% and 90% yields, respectively. Benzil is obtained by the same reaction in yields of 30—40%.

A solution of the ketol (5 g.) and nitrobenzene (4 g.) in 50 c.c. of alcohol containing 2 c.c. of 6% alcoholic sodium ethoxide was boiled under reflux for 2—3 minutes and then allowed to cool. The diketone which separated, recrystallised from alcohol, gave 4 g. of anisil, m. p. 133°, in the case of anisoin, and 4·7 g. of furil, m. p. 162°, in the case of furoin.

The author again desires to thank Prof. A. A. Boon for his interest in the work and for providing facilities for its prosecution.

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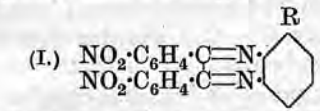
CCXLVIII.—*Some Reactions of* mm′-*Dinitrobenzil.*

By Alfred Archibald Boon and Hugh Bryan Nisbet.

The *mm*′-dinitrobenzil used in this research was prepared by direct nitration of benzil (Barrett and Kay, *Chem. News*, 1922, **125**, 57) and was separated from the accompanying *om*′- and *oo*′-isomerides by fractional crystallisation from acetone (compare Chattaway and Coulson, J., 1926, 1071), or by isolating the molecular *compound* with benzidine and decomposing that with dilute acid (see below).

mm′-Dinitrobenzil readily responds to the usual reactions for *o*-diketones : when treated in hot alcoholic solution with *o*-diamines it yields the corresponding quinoxalines, *e.g.*, 2 : 3-*di*-m-*nitrophenylquinoxaline* (I; R = H) and 5-*methylquinoxaline* (I; R = Me) with *o*-phenylene- and *o*-tolylene-diamine, respectively.



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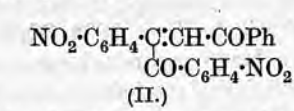

(II.)

Ferriss and Turner (J., 1920, **117**, 1143) and Le Fèvre and Turner (J., 1926, 2480) have disproved Cain and Micklethwait's work on the condensation of benzil with benzidine (J., 1914, **105**, 1437), and have shown that in glacial acetic acid solution 1 mol. of benzidine unites with 2 mols. of benzil, with the elimination of 2 mols. of water. *mm*′-Dinitrobenzil does not condense with benzidine in glacial acetic acid solution, but in hot alcoholic solution equimolecular proportions unite to form a compound which is quantitatively decomposed into its components by acetic acid or dilute mineral acid. A similar molecular *compound* is formed with *o*-tolidine.

mm′-Dinitrobenzil condenses with a molecular proportion of acetophenone under the influence of alcoholic caustic soda to give *dehydroacetophenone*-mm′-*dinitrobenzil* (α-m-*nitrobenzoyl*-β-*benzoyl*-m-*nitrostyrene*) (II). A compound with 2 mols. of acetophenone could not be isolated, nor could any crystalline product be obtained in many attempts to condense *mm*′-dinitrobenzil with acetone.

Experimental.

Preparation of Quinoxalines.—Equimolecular quantities of *mm*′-dinitrobenzil and the corresponding diamine were dissolved in alcohol, and the solution was boiled for about twenty minutes. The quinoxalines which separated were filtered off and recrystallised from a large quantity of alcohol. 2 : 3-*Di*-m-*nitrophenylquinoxaline* formed white needles, almost insoluble in alcohol, m. p. 208° (Found : C, 64·2; H, 3·3; N, 15·0. $C_{20}H_{12}O_4N_4$ requires C, 64·5; H, 3·2; N, 15·1%); and 2 : 3-*di*-m-*nitrophenyl*-5-*methylquinoxaline* formed

pale yellow needles, slightly soluble in ether, and soluble in warm acetone or benzene, m. p. 208—210° (Found: C, 64·1; H, 3·6; N, 14·4. $C_{21}H_{14}O_4N_4$ requires C, 65·3; H, 3·7; N, 14·5%).

Molecular Compound of mm'*-Dinitrobenzil and Benzidine.*—When equimolecular quantities of *mm'*-dinitrobenzil and benzidine, dissolved in absolute alcohol, were boiled for a few minutes, a crystalline compound was formed; it recrystallised from alcohol as chocolate-brown plates, m. p. 163·5°, yield almost theoretical [Found: C, 64·3, 64·3; H, 4·5, 4·5; N, 11·4; NO_2 (by $TiCl_3$), 19·0. $C_{26}H_{20}O_6N_4$ requires C, 64·5; H, 4·5; N, 11·6; NO_2, 19·0%]. This *compound* is readily decomposed into its constituents by acetic acid or dilute mineral acids, and when decomposition was effected by dilute hydrochloric acid, the *mm'*-dinitrobenzil, after being washed with water and dried, corresponded to 59·0% of the initial material (Calc.: 60·2%). Cryoscopic measurements in 2 : 4-dinitrotoluene (Auwers, *Z. physikal. Chem.*, 1899, **30**, 310) gave $M = 258$, showing that the molecular compound is almost completely dissociated in that solvent.

Isolation of mm'*-dinitrobenzil by means of its benzidine compound.* Benzil was nitrated by Barrett and Kay's method (*loc. cit*), and the mixed nitro-compounds were boiled with a solution of sodium carbonate to remove nitro-acids; 25 g. of the resulting mixture were dissolved in 400 c.c. of boiling alcohol, and 18 g. of pure benzidine added. The chocolate-brown crystalline deposit formed after a few minutes' boiling was filtered from the hot liquid and proved to be the foregoing addition compound (crude yield, 18 g., m. p. 163·5°). When decomposed with acetic acid containing a little hydrochloric acid, it gave 10 g. of a yellow substance, m. p. 126°, which, recrystallised from acetone and then from glacial acetic acid, gave tufts of pale yellow needles, m. p. 132°, identical with the *mm'*-dinitrobenzil isolated by Chattaway and Coulson's method (*loc. cit.*).

Molecular Compound of mm'*-Dinitrobenzil and* o*-Tolidine.*—Equimolecular quantities of the two constituents in hot alcohol yield a molecular *compound* which, recrystallised from alcohol containing a little *o*-tolidine, forms chocolate-coloured plates, m. p. 164° (Found: N, 11·2. $C_{28}H_{24}O_6N_4$ requires N, 10·94%).

*Dehydroacetophenone-*mm'*-dinitrobenzil* (II).—*mm'*-Dinitrobenzil (8 g.) and acetophenone (6·4 g.) were dissolved in warm alcohol, and 2 c.c. of *N*/10-alcoholic caustic soda added. The solid which separated on cooling and standing was washed with dilute hydrochloric acid, and separated from benzene in fine yellow needles, m. p. 158° (Found: C, 65·86; H, 3·48; N, 6·64. $C_{22}H_{14}O_6N_4$ requires C, 65·69; H, 3·47; N, 6·94%).

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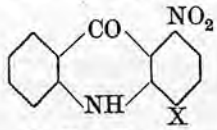
418. *The Reactivity of Groups in Substituted Acridones. Part I. Replacement of Nitro-groups by Piperidyl and Piperazyl.*

By HUGH B. NISBET and (in part) ADAM B. GOODLET.

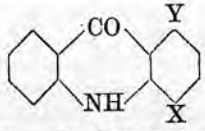
NUMEROUS cases, *e.g.*, *o*- and *p*-dinitrobenzenes, 4-chloro-1 : 2-dinitrobenzene, are known in which one of two cationoid groups in an aromatic nucleus, ortho or para to each other, is replaced when attacked by an anionoid reagent.

That the carbonyl group in anthraquinone acts as a cationoid group is shown by the facts that 1-chloroanthraquinone gives 1-piperidylanthraquinone when heated with piperidine (D.R.-P. 136777), the nitro-group in 1-nitroanthraquinone may be replaced by the methylamino- (D.R.-P. 144634), dimethylamino-, or piperidyl group (D.R.-P. 136777), and in 4-chloro-1-nitroanthraquinone both the nitro-group and the chlorine atom are replaced on heating with *p*-toluidine (D.R.-P. 126803).

It has now been found that in the reaction between piperidine or piperazine and 1-halogeno-4-nitroacridones (I) the *p*-nitro-group,



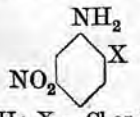
(I; X = Cl or Br)



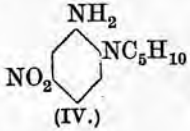
(II; Y = piperidyl or piperazyl)

instead of activating the halogen atom and facilitating its replacement by the negative reagent, is itself replaced, the product being (II).

The activating influence of the *o*-carbonyl group on the nitro-group in the acridone ring may be inferred from the similarity to the reactions in the anthraquinone series. Further, that the removal of the heterogeneous polarity caused by the two cationoid groups (CO and NO_2) ortho to one another proceeds more readily than the replacement of activated halogen may be inferred, since such reaction takes place in this case, whereas in 2-halogeno-5-nitroanilines (III), in the absence of heterogeneous polarity, the removal of halogen by piperidyl to give 5-nitro-2-piperidylaniline (IV) proceeds normally on heating in a sealed tube.



(III; X = Cl or Br.)



(IV.)

Experimental.

Nitration of o-*Chloro*(or *Bromo*)*aniline.*—KNO_3 (1 mol.; 1 part) in H_2SO_4 (*d* 1·84; 37 parts) was added to the base (1 mol.) in H_2SO_4 (30—37 parts) at 0—2° during ½ hr. The mixture was poured on ice (60 parts) and then into H_2O (800 parts). 2-Chloro- and 2-bromo-5-nitroaniline were obtained from spirit in yellow needles, m. p. 117° (yield, 52%) and 138° (yield, 70%) respectively.

Acridone Formation.—The above 2-halogeno-5-nitroanilines (1/50 g. mol.), K *o*-bromobenzoate (1/50 g.-mol.), amyl alcohol (10 c.c.), and Cu powder (0·1 g.) were heated under reflux for 4 hr., the mixture made alkaline with NaOH, the alcohol distilled in steam, the residue cooled, and the filtered solution acidified with dil. HCl. The yellow ppt., cryst. from AcOH, gave the 2-halogeno-5-nitrodiphenylamine-6′-carboxylic acids. These were heated on a steam-bath with H_2SO_4 (*d* 1·84; 12—14 parts) for 15—20 min., the solution poured into H_2O, and the solid which separated boiled with H_2O, then with dil. Na_2CO_3 aq., and again with H_2O, and crystallised from much AcOH.

2-Chloro-5-nitrodiphenylamine-6′-carboxylic acid formed golden-yellow needles (yield, 40%), m. p. 260—261° (Found : N, 9·8. $C_{13}H_9O_4N_2Cl$ requires N, 9·6%), and *2-bromo-5-nitrodiphenylamine-6′-carboxylic acid* brownish-orange needles (yield, 34%), m. p. 252° (Found : Br, 24·2. $C_{13}H_9O_4N_2Br$ requires Br, 23·7%).

1-Chloro-4-nitroacridone (I; X=Cl) formed yellow needles (yield, 64%), m. p. 320° (Found : N, 10·0. $C_{13}H_7O_3N_2Cl$ requires N, 10·2%), and *1-bromo-4-nitroacridone*, lemon-yellow needles (yield, 55%), m. p. 305° (Found : Br, 24·9. $C_{13}H_7O_3N_2Br$ requires Br, 25·1%).

Action of Piperidine or Piperazine on 1-Halogeno-4-nitroacridones.—The acridone (1 part) was gently refluxed with piperidine (approx. 5 parts) or piperazine (approx. 2½ parts) until it dissolved (about 1 hr.), the solution poured into cold H_2O, and the ppt. crystallised from dil. EtOH.

1-Chloro-4-piperidylacridone (II; X = Cl, Y = $C_5H_{10}N$) formed yellow needles, m. p. 110° (Found : N, 8·9; Cl, 11·1. $C_{18}H_{17}ON_2Cl$ requires N, 9·0; Cl, 11·3%); the hydrochloride, pptd. by dry HCl from $CHCl_3$, crystallised from H_2O in yellow needles, m. p. 168—169°.

1-Bromo-4-piperidylacridone formed bright yellow needles, m. p. 112° (decomp.) after softening at 98—102° (Found : Br, 21·6. $C_{18}H_{17}ON_2Br$ requires Br, 22·4%); the hydrochloride had m. p. 164—165°.

1-Chloro-4-piperazylacridone formed brownish-yellow needles, m. p. 197—198° (Found : N, 13·8; Cl, 10·3. $C_{17}H_{16}ON_3Cl$ requires N, 13·4; Cl, 11·3%).

Action of Piperidine on 2-Halogeno-5-nitroanilines.—Piperidine at its b. p. had little action on the halogenonitroanilines. 2-Chloro-5-nitroaniline (6·88 g.) and piperidine (7 c.c.) were heated in a sealed tube at 180° for 6 hr., and the product poured into H_2O (400 c.c.). The oil obtained, after solidifying, was crystallised twice from spirit, giving *2-piperidyl-5-nitroaniline* in chocolate-brown needles (3·3 g.), m. p. 79—81° (Found : N, 19·4. $C_{11}H_{15}O_2N_3$ requires N, 19·0%).

The authors thank Dr. W. O. Kermack for his interest in this investigation.

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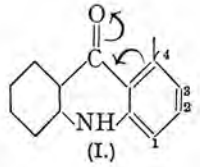
319. *The Reactivity of Groups in Substituted Acridones. Part II. Cationoid Activity at Position 4 in Acridones.*

By Hugh B. Nisbet.

The cationoid activity previously found (J., 1932, 2772) in acridones (I) at position 4 has now been confirmed by the demonstration that halogen substituted there is readily replaced by anionoid reagents : from 1 : 4-dihalogenoacridones (II; X and Y = Cl or Br) the halogen (Y) is removed by piperidine, 1-halogeno-4-piperidinoacridones being produced identical with the compounds already obtained by the removal of the nitro-group from 1-halogeno-4-nitroacridones (*loc. cit.*) and in better yield than by the latter method.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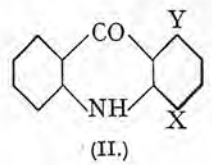
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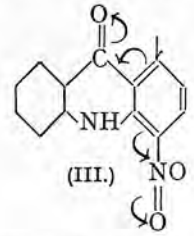
(III.)

4-Chloro-1-methylacridone (II; X = CH_3, Y = Cl) is unchanged even on heating for a long time with piperidine. This is in agreement with the effect of a methyl group on substitution and replacement in the benzene ring, *i.e.*, facilitating cationoid and retarding anionoid attack.

Bradley and Robinson (J., 1932, 1255) have shown that even hydrogen may be replaced by piperidino in such compounds as nitrobenzene, which yields *p*-piperidinonitrobenzene. The somewhat similar case of 1-nitroacridone, where the cationoid effects of the nitro- and the carbonyl group will be cumulative (III), might be expected to yield 1-nitro-4-piperidinoacridone. No such reaction took place on heating with excess of piperidine in the presence of sodamide. 1-Nitro-4-piperidinoacridone is readily obtained, however, by treating 4-chloro-1-nitroacridone with piperidine.

Experimental.

The following substituted diphenylamine-6′-carboxylic acids have been prepared from the requisite substituted aniline and potassium *o*-bromobenzoate, and converted into the undernoted corresponding acridones by the methods already described (*loc. cit.*).

2 : 5-Dichlorodiphenylamine-6′-carboxylic acid formed greyish-white needles (yield, 48%), m. p. 232° (Found : Cl, 24·4. $C_{13}H_9O_2NCl_2$ requires Cl, 25·1%), *2 : 5-dibromodiphenylamine-6′-carboxylic acid* greyish-white needles (yield, 36%), m. p. 229—230° (Found : Br, 42·8. $C_{13}H_9O_2NBr_2$ requires Br, 43·1%), and *5-chloro-2-methyldiphenylamine-6′-carboxylic acid* lemon-coloured needles (yield, 60%), m. p. 180—181° (Found : Cl, 13·0. $C_{14}H_{12}O_2NCl$ requires Cl, 13·1%).

5-Chloro-2-nitrodiphenylamine-6′-carboxylic acid, which was best prepared from potassium anthranilate and 2 : 4-dichloronitrobenzene, was found to be dimorphous—yellow needles and reddish cubic plates, both m. p. 228°. The reddish cubic plates, when crystallised quickly from glacial acetic acid, were converted into the yellow needle form (Found : Cl, 11·9. $C_{13}H_9O_4N_2Cl$ requires Cl, 12·1%).

1 : 4-Dichloroacridone formed microcrystalline yellowish needles (yield, 64%), m. p. 268° (Found : Cl, 26·4. $C_{13}H_7ONCl_2$ requires Cl, 26·9%), *1 : 4-dibromoacridone* pale yellow needles (yield, 55%), m. p. 232—233° (Found : Br, 44·8. $C_{13}H_7ONBr_2$ requires Br, 45·3%), and *4-chloro-1-methylacridone* small, pale yellow needles (yield, 75%), m. p. 298° (Found : Cl, 14·5. $C_{14}H_{10}ONCl$ requires Cl, 14·5%). *4-Chloro-1-nitroacridone* crystallised from nitrobenzene in reddish tabular plates, m. p. 240° (Found : Cl, 13·2. $C_{13}H_7O_3N_2Cl$ requires Cl, 13·0%).

By the action of piperidine on the above acridones under the conditions given in the previous communication the following 4-piperidinoacridones have been obtained : 1-chloro-4-piperidinoacridone (yield, 77%), 1-bromo-4-piperidinoacridone (yield, 89%),and *1-nitro-4-piperidinoacridone*, which formed fine orange-yellow needles (yield, almost theoretical), m. p. 192° (Found :

N, 13·3. $C_{18}H_{17}O_3N_3$ requires N, 13·0%). The first two showed no depression in m. p. in admixture with those already described.

The author thanks the Carnegie Trust for the Universities of Scotland for a grant.

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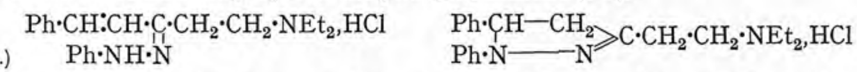
206. *Heterocyclic Ketones. Part I. β-Amino-ketones and Related Pyrazolines derived from Benzylidene- and Furfurylidene-acetone.*

By HUGH B. NISBET and CECIL G. GRAY.

MANNICH and SCHÜTZ (*Arch. Pharm.*, 1927, **265**, 684) have described the condensation of arylidene ketones (I) with formaldehyde and secondary base hydrochlorides as a method of preparing β-amino-ketones of the type (II).

$$\underset{\text{(I.)}}{R'{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_3} + CH_2O + NHR_2{,}HCl \longrightarrow \underset{\text{(II.)}}{R'{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NR_2{,}HCl} + H_2O$$

Benzylideneacetone (I; R′ = Ph) by this reaction gave with diethylamine hydrochloride and formaldehyde 1-diethylamino-5-phenyl-Δ^4-penten-3-one (II; R′ = Ph, $R_2 = Et_2$), from which these authors prepared the phenylhydrazone (III).

(III.)  (IV.)

Now, as the phenylhydrazones of α-unsaturated ketones change easily and sometimes uncontrollably into pyrazolines, the so-called phenylhydrazone (III) might be the isomeric pyrazoline (IV). It has now been shown, however, that the substance, although giving a positive test for pyrazoline by Knorr's reaction (which is not infallible, since it is given by phenylhydrazones containing only a trace of pyrazoline); gives aniline on reduction and must therefore actually be the phenylhydrazone (III).

When the compound (III) was boiled with acetic acid, the colour change characteristic of the conversion of phenylhydrazone into pyrazoline occurred, but the new pyrazoline could not be isolated. The phenylhydrazone of the piperidino-compound (II; R′= Ph, $R_2 = NC_5H_{10}$) was converted by such treatment into the corresponding *pyrazoline*, which was isolated.

In an analogous manner from furfurylideneacetone 1-*dimethylamino*-, 1-*diethylamino*-, and 1-*piperidino*-5-*furyl*-Δ^4-*penten*-3-*one* have been prepared (as hydrochlorides). The *phenylhydrazones* of the dimethylamino- and the piperidino-compound respectively have also been prepared and the latter has been converted into the isomeric 1-*phenyl*-3-(β-*piperidinoethyl*)-5-*furylpyrazoline hydrochloride*. The former gives the characteristic colour change on boiling with glacial acetic acid, but the pyrazoline could not be isolated.

EXPERIMENTAL.

1 : 5-*Diphenyl*-3-(β-*piperidinoethyl*)*pyrazoline*.—The phenylhydrazone of 1-piperidino-5-phenyl-Δ^4-penten-3-one hydrochloride (5·1 g.) and acetic acid (25 c.c.) were boiled under reflux for a few hours and the dark green solution was then treated with excess of sodium hydroxide. Ether extracted the *base*, which was obtained (nearly 2 g.) from light petroleum as a pale yellow solid (peculiar odour), m. p. 60° (Found : N, 12·7. $C_{22}H_{27}N_3$ requires N, 12·6%).

1-*Dimethylamino*-5-*furyl*-Δ^4-*penten*-3-*one Hydrochloride*.—The vigorous reaction which set in almost immediately when furfurylideneacetone (6·8 g.), dimethylamine hydrochloride (4·1 g.), and paraformaldehyde (2·1 g.) in alcohol (5 c.c.) were warmed gently under reflux, was completed by a few minutes' boiling. The solid obtained on cooling crystallised from alcohol in pale yellow leaves, m. p. 170° (mixed m. p. with dimethylamine hydrochloride, 120—130°) (Found : N, 6·3; Cl, 15·0. $C_{11}H_{16}O_2NCl$ requires N, 6·1; Cl, 15·5%). The *phenylhydrazone*, prepared by the method of Auwers and Voss (*Ber.*, 1909, **42**, 4411), formed long yellow needles from 95% alcohol; m. p. 185° (Found : N, 13·4; Cl, 11·2. $C_{17}H_{21}ON_3$,HCl requires N, 13·15; Cl, 11·2%).

The following compounds were prepared by analogous methods, except that in the preparation of the β-amino-ketones a second portion of paraformaldehyde (1 g.) was added to the reaction mixture and the heating continued for some time to complete the reaction.

1-*Diethylamino*-5-*furyl*-Δ^4-*penten*-3-*one hydrochloride*, brownish hexagonal needles from aqueous acetone; m. p. 125° (Found : N, 5·5. $C_{13}H_{19}O_2N$,HCl requires N, 5·4%).

1-*Piperidino*-5-*furyl*-Δ^4-*penten*-3-*one hydrochloride* crystallised from alcohol in pale yellow, cubic plates which darkened on exposure to light; m. p. 192° (with darkening) (Found : N, 5·3; Cl, 12·9. $C_{14}H_{19}O_2N$,HCl requires N, 5·19; Cl, 13·17%). The *phenylhydrazone* formed long, dark yellow needles from alcohol; m. p. 182° (Found : N, 11·9; Cl, 9·6. $C_{20}H_{25}ON_3$,HCl requires N, 11·7; Cl, 9·9%).

1-*Phenyl*-3-(β-*piperidinoethyl*)-5-*furylpyrazoline Hydrochloride*.—1·5 G. of the phenylhydrazone were heated under reflux with acetic acid (8 c.c.) for ½ hour. The *pyrazoline hydrochloride*, obtained on cooling, crystallised from alcohol in almost colourless needles, m. p. 158° (Found : N, 11·5; Cl, 9·0. $C_{20}H_{25}ON_3$,HCl requires N, 11·7; Cl, 9·9%).

One of us (H. B. N.) thanks the Carnegie Trust for the Universities of Scotland for a grant.

HERIOT-WATT COLLEGE, EDINBURGH. [*Received, May 16th*, 1933.]

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SOME SYNTHETICAL EXPERIMENTS ON ORGANIC BASES.

CONTENTS.

INTRODUCTION.

The Thesis now presented is an account of some work undertaken by the Author with the primary object of preparing bases suitable for test as anti-malarials but deals in some detail with some important observations which have resulted from difficulties encountered in the course of the work.

Malaria has long taken its toll of human life and added to the sufferings of humanity. The fever known to the ancients had its cause only fully revealed towards the end of last century when Sir Ronald Ross traced the life history of the parasite which for the full cycle of its activity requires both animal and human hosts.

Three forms of the causative organism of this protozoal disease are recognised:-

Plasmodium vivax, which causes benign tertian malaria,
" malaria, which causes quartan malaria,
and " falciparum, which causes malignant malaria.

The plasmodium is transmitted to the human host by the bite of the mosquito as a minute spindle-shaped cell or sporozoite which invades a red blood-cell. Here it develops and when fully grown the trophozoite so formed undergoes shizogony. A group of merozoites results from this change and when these are liberated into the blood stream by rupture of the corpuscular envelope the characteristic febrile paroxysm occurs. The merozoites invade fresh red corpuscles and the asexual cycle is repeated. The length of time the organism takes to develop varies with the species:-

P. vivax ..... Two days
P. malaria ..... Three days
P. falciparum ..... One or two days

and this governs the recurrence of the fever. The mechanism of transmission of the disease depends on the fact that while

some/

some of the organisms develop into shizonts others change into male and female gametocytes which remain unchanged in human blood. When withdrawn by a mosquito, however, they undergo various changes in the stomach and body-cavity of these anopheles finally settling in the salivary gland from which the sporozoites are injected with the salivary secretion when the insect bites a human subject.

No effective treatment for the victims of the disease was known till cinchona bark was brought to Europe about 300 years ago. It is related that the Countess of Chinchon, wife of the Viceroy of Peru, was cured of tertian fever by use of Peruvian bark in 1638 and returning to Spain shortly after her recovery brought with her samples of this bark which she administered to the malaria stricken peasants on her estate.

From the time of its discovery to the middle of the eighteenth century all the bark was drawn from the forests of Loxa on the Ecuador-Peru frontier. About 1852 an era of scientific transplantation and cultivation commenced and now almost all tropical and semi-tropical countries are capable of producing some of the forms of cinchona bark.

In 1810, Gomez, a Portuguese Naval surgeon, separated cinchonine from the bark; ten years later Pelletier and Cavantou isolated quinine, and by 1850 cinchonidine and quinidine had been obtained. Up to the present time some thirty alkaloids have been isolated from natural cinchona barks.

The Royal Commission of 1867 in its report on the comparative efficiency of the alkaloids in dealing with the Indian malaria problem placed the most important in order, of/

of descending value:-

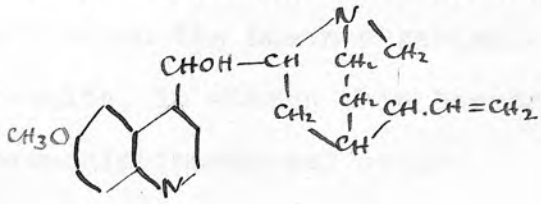
1st. Quinine and Quinidine

3rd. Cinchonidine

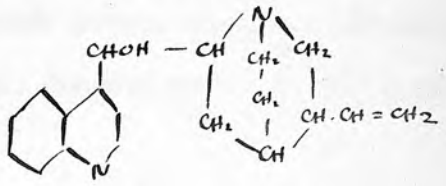
4th. Cinchonine

The fact that the world's consumption of quinine today is approximately 600 tons shows how important this drug is in the fight against malaria.

The chemical constitutions of quinine and cinchonine have been investigated by Skraup, Koenigs, Rabe and others, and the following formulae have been suggested for them:-



Quinine



Cinchonine

Quinidine and cinchonidine are probably stereoisomeric with quinine and cinchonidine respectively. Dihydroquinine and dihydrocinchonine have been synthesised by Rabe and Kinder (Ber., 1918, 51, 1360).

When the League of Nations set up its Malaria Commission in 1923, the object of which was to discover how it might be possible to provide treatment for poverty-stricken victims of malaria, it is significant that at that time treatment was synonymous with "quinine". During the last ten years, however, there has been more development in the study of the disease, its cause and treatment, than during all the hundreds of years that humanity has suffered the scourge of Ague.

During the last decade a routine method was devised by the late Dr. Roehl for testing derivatives of quinine and quinoline for anti-malarial activity on canaries infected with/

with bird malaria. This has lead to the discovery of synthetic preparations which give the promise of being more effective therapeutic and prophylactic agents than quinine. At the same time a more careful study of the effect of quinine on the malarial parasite has shown that it has its limitations as an anti-malarial. Quinine appears to have most action on the young merozoites i.e. at the stage when they are set free in the blood stream, and thus prevents the febrile paroxysm in the victim; but the drug is without action on the gametocytes. Not only so, but quinine is not without action on the human organism - in some cases chronic poisoning results, in others skin haemorrhages, haemolysis or serious haemoglobinuria may occur.

Quinidine is considered as good as, or perhaps slightly better than, quinine while cinchonidine and cinchonine are definitely inferior when used in small doses. Dihydroquinine, which occurs naturally in cinchona bark and has been synthesised (Rabe, loc. cit.), has been found to be superior to quinine both as regards its tolerability by the human subject and its parasiticidal action.

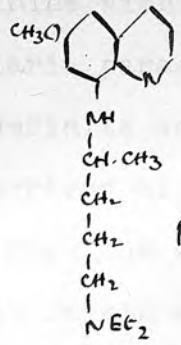
Plasmoquin, (N-diethylamino-isopentyl-8-amino-6-methoxy-quinoline), the first effective anti-malarial drug, has been found to have a specific action on the gametocytes and is most suitable as a gametocide in malignant tertian malaria. Like quinine, however, it is not without action on the human organism.

The fact that plasmoquin acts on the gametocytes and that quinine acts on the merozoites resolved the chemo-therapeutic problem into a four-fold one - the discovery of drugs which act on (a) sporozoites (b) asexual forms (c) sexual forms and (d) forms responsible for relapses, perhaps singly

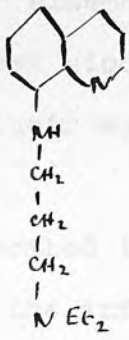
in/

in the first instance but finally a specific which will act on any or all of the four stages.

Fourneau 710, the constitution of which in relation to plasmoquin is noted below, is somewhat more toxic than plasmoquin



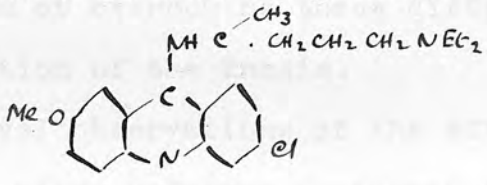
Plasmoquin.



Fourneau 710.

but has about the same gametocidal power.

Atebrin, (Erion), the dihydrochloride of 7-methoxy-2-chloro-5-δ-diethylamino-δ-pentyl-aminoacridine* (Mauss and Meitsch, Klin. Woch., 1933, 12, 1276), is a yellow crystalline solid which unlike plasmoquin is relatively non-toxic; the minimum lethal dose given by mouth to rabbits, cats and mice is about the same as that of quinine.



Atebrin.

In man the only disagreeable effects reported seem to be epigastric pains in a few cases, feelings of excitement and lightheadedness (rare) and yellow staining of the skin and urine in most persons who have taken the drug daily for five or more days. Atebrin is not capable of bringing about the complete sterilisation of the malaria parasite in the human host but it certainly has a more powerful action in preventing relapses of malignant tertian malaria than any remedy previously/

*See Note on Nomenclature on page 7.

previously known.

Stovarsol, N-acetyl-4-hydroxy-m-arsanilic acid, has been reported to have a definite action on the benign tertian parasite, P. vivax, but without action on the parasites of quartan and malignant tertian fever. The action of mixtures of quinine with stovarsol, and of plasmoquin with quinine on malaria parasites have also been studied but as yet no very definite conclusions as to their applicability have been arrived at.

When the work which is described in the first section of this Thesis was begun not all the information which is given above was to hand. The formula for plasmoquin and its great potency as a gametocide had just been made known when the Author was attracted by the problem of the synthesis of the acridine analogue or, at any rate, of simple aminoalkyl-aminoacridines with the side chain in the 1- position. Difficulties were encountered, some of which have not yet been surmounted, and the investigations which have come out of the problem of overcoming these difficulties constitute the major portion of the Thesis.

Some novel observations of the action of bases such as piperidine on nitro-halogeno-acridones in which it was presumed that activated halogen would be replaced by piperidyl showed that the nitro group was the one which was replaced. This led to a careful study of the modern theories of substitution in the benzene ring - a problem which has received a great deal of attention since the introduction of the electronic theory of valency and which has been elaborated with care and thoroughness by Robinson and his collaborators and by Ingold and his co-workers. An attempt to correlate substitution and replacement in the aromatic nucleus is made in/

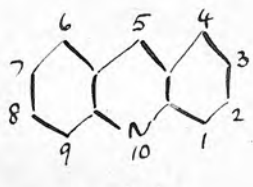
in Part IV of the Thesis.

It was necessary for the preparation of nitro-halogenated acridones to devise a method for the preparation of nitro-halogenated anilines and the investigations on this subject are treated in Part II. Part V deals with some synthetical experiments on Schiff's bases derived from 2-aminodiphenyl-amine-6'-carboxylic acid and 2-aminodiphenylamine. The thermal decomposition of the simple benzylidine derivative of the latter gave a compound which is regarded as 1-anilino-acridine.

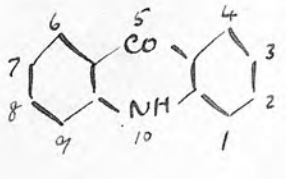
During the course of the investigations now described it has been possible to prepare some acridine derivatives suitable for testing as anti-malarials and these along with other compounds (the preparations of which have been described in other publications by the Author) submitted to the Chemotherapy Committee for such test are listed in Appendix I. Appendix II gives a list of papers published by the Author and submitted as additional evidence in support of his candidature for the degree of Doctor of Philosophy of Edinburgh University.

Note on Nomenclature.

The numbering used for derivatives of acridine and acridone described in this Thesis is indicated in the formulae noted below:-



Acridine

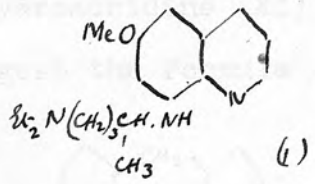


Acridone.

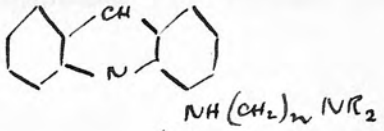
PART 1.

ATTEMPTS to SYNTHESISE ANTI-MALARIALS.

As has been pointed out in the Introduction part of the work which is described in this Thesis was carried out with the object of preparing compounds suitable for testing as anti-malarials. It was thought that the acridine analogues of plasmoquin (1) would be suitable substances and attempts have been made to obtain compounds such as (11).

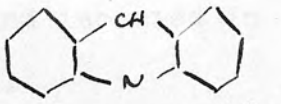


(I)



(II).

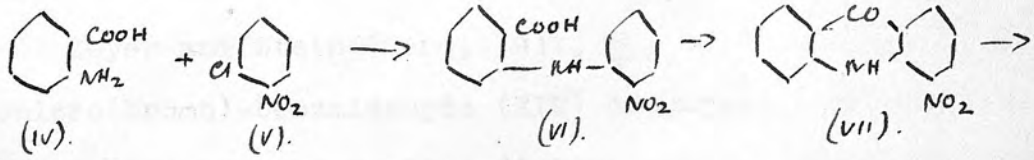
The obvious starting material was 1-(9)-amino-acridine (111)

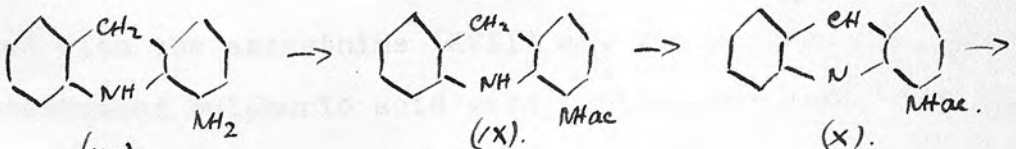


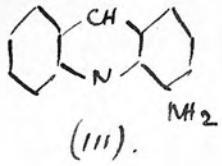
(III).

which has been prepared by Clemo, Perkin, and Robinson (J.C.S., 1924, 1784) by the following outline synthesis:-

SYNTHESIS 1.

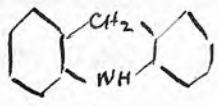






(III).

The repetition of this synthesis worked excellently as far as 1-nitro-acridone (VII) but the following stage i.e. reduction with sodium amalgam in alcohol in the presence of sodium bicarbonate and in a stream of carbon dioxide, in spite of many attempts, has so far been found impracticable. From the mixture obtained on reduction only one compound has been isolated in small quantity in a state of purity but the analysis gives little clue to its identity. The fact that the compound contains a small percentage of oxygen suggests that it may be some curious substance analogous to that obtained by Lehmstedt and Hundertmark (Ber., 1929, 62, 414-418) by sodium amalgam reduction of acridine. In addition to dihydroacridine (XI) they got a compound for which they suggest the formula (XII).



(XI).

$C_{13}H_{10}>NH$
$C_{13}H_{10}>NH$ $>O$

(XII).

$C_{13}H_{12}N>NH$
$C_{13}H_{12}N>NH$ $>O$

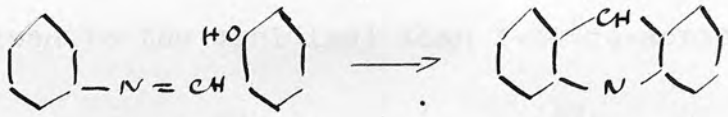
(XIII).

By analogy the compound isolated in the reduction of 1-nitro-acridone may be (XIII).

Failure at this vital stage in this synthesis led to the investigation of other methods of preparing 1-nitro-acridine which, being much more soluble than 1-nitro-acridone and devoid of the carbonyl group, would conceivably be easier to reduce.

Meyer and Stein (Ber., 1917, 50, 1312) claimed that o-chloro(bromo)-benzaldehyde (XIV) condensed with o-nitro-aniline (XV) to give 2-nitro-diphenylamine-6'-aldehyde (XVI) mixed with the azomethine (XVII) and the mixture treated with concentrated sulphuric acid gave 1-nitro-acridine (XVIII).

gave acridine (XXIII). An attempt was made to prepare salical-o-nitro-aniline (XXIV) which on similar treatment might be expected to give 1-nitro-acridine.



(XXII). (XXIII).

THESIS 4.

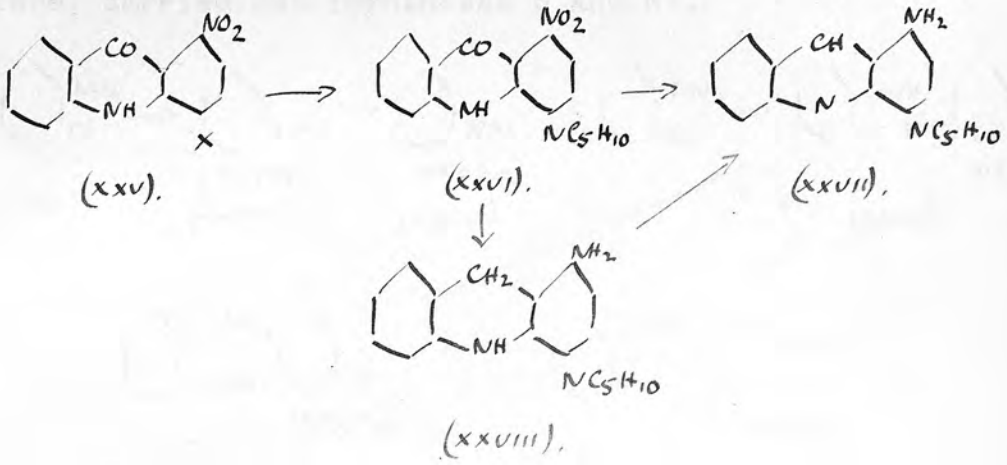
(XXIV). (XXV).

This failed, however, owing to the difficulty of forming the required azomethine. It is to be noted in this connection that Meyer and Stein (loc. cit.) state that the presence of the o-nitro group in aniline hinders azomethine formation.

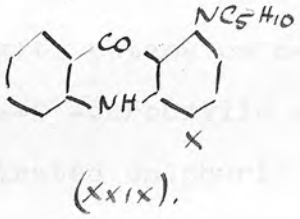
The direct nitration of acridine (XXIII), of course, might be regarded as the most obvious and direct method of preparing the desired 1-nitro-acridine. Investigations of the nitration of acridine by Graebe and Caro (Ann., 158, 275) and in more detail by Jensen and Friedrich (loc. cit.) have shown that this reaction gives a mixture of 2-nitro-acridine with 1-nitro-acridine. The latter substance is obtained only in small quantity and with considerable difficulty. So that this possibility had to be ruled out.

It was next regarded as possible to synthesise 1-halogeno-4-nitro-acridones (XXV) in which it might be expected that the halogen atom activated by the para nitro group/

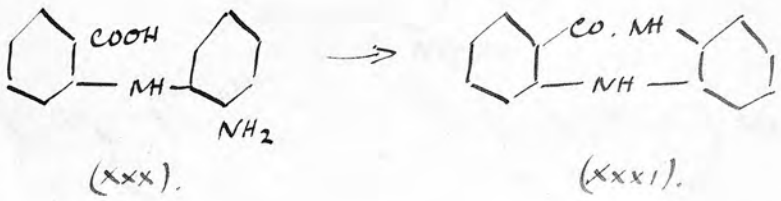
group would be replaceable by anionoid groups (NH_2; $NHEt_2$; $NHMe_2$; NHC_5H_{10} etc.,) to give a basic compound such as (XXVI) and this might be more easily reduced to the acridine (XXVII) or the dihydroacridine (XXVIII) (which could be oxidised to the acridine) than 1-nitro-acridone had proved.



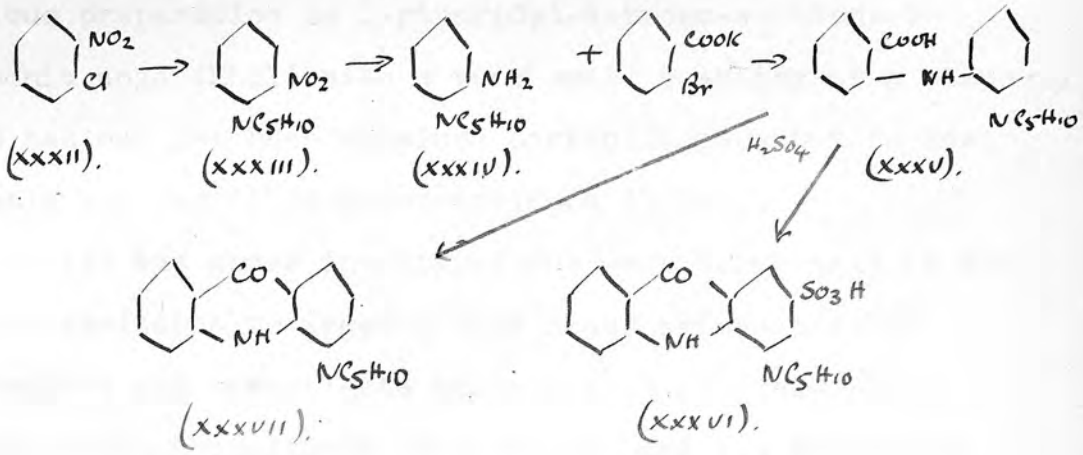
It was found, however, (as recorded in Part III of this Thesis) that the nitro group was replaced by the anionoid group to give, say with piperidine, 1-halogeno-4-piperidyl-acridone (XXIX).



The next obvious step was to replace the halogen atom by the anionoid group before closing the acridone ring. The type of anionoid group had to be carefully chosen since, as Clemo, Perkin and Robinson (J.C.S., 1924, 1779) have shown 2-amino-diphenylamine-6'-carboxylic acid (XXX) easily loses water to yield the anhydro-acid (XXXI).



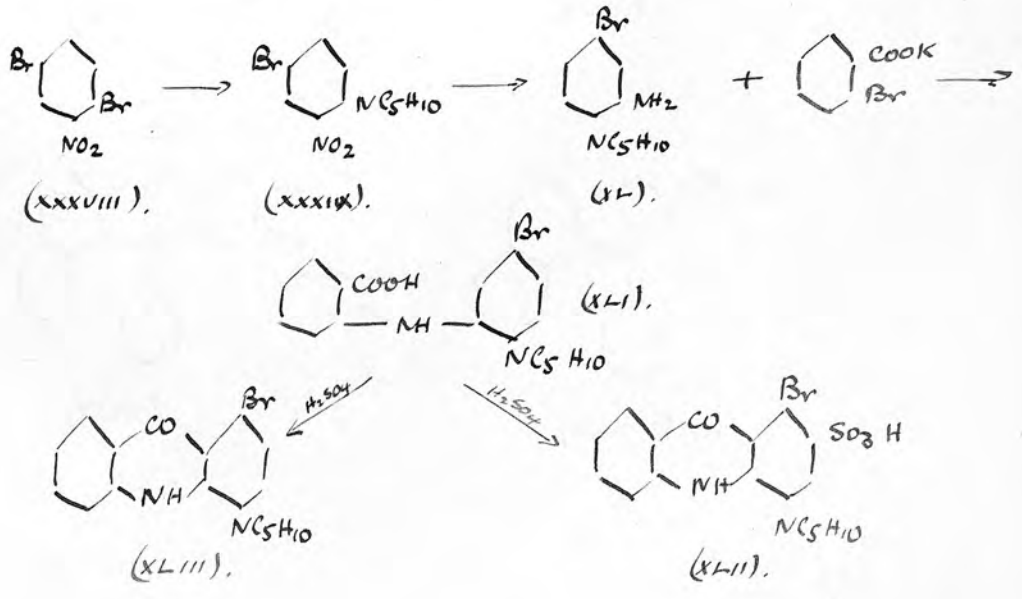
The replacement of halogen by primary or secondary amino groups before acridonation was thought, therefore, likely to lead not to an acridone but to some derivative of the anhydro-acid. Replacement by a tertiary nitrogen was expected to yield the desired compounds. The following syntheses were, therefore, carried out (Syntheses 5 and 6).



(XXXII). (XXXIII). (XXXIV). (XXXV). (XXXVII). (XXXVI).

SYNTHESIS 5.

o-Piperidyl-nitrobenzene (XXXIII) was prepared by the action of piperidine on o-nitro-chlorobenzene: this was reduced by West's method (J.C.S., 1925, 494) to give o-piperidyl-aniline (XXXIV) which condensed with potassium o-bromobenzoate to give 2-piperidyl-diphenylamine-6'-carboxylic acid (XXXV). This on treatment with concentrated sulphuric acid gave as main product the sulphonic acid (XXXVI), and only in small quantity the desired 1-piperidyl-acridone (XXXVII) (isolated as acetate).

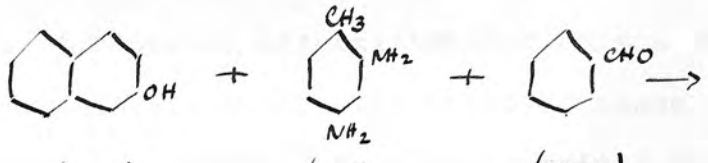


(XXXVIII). (XXXIX). (XL). (XLI). (XLIII). (XLII).

SYNTHESIS 6.

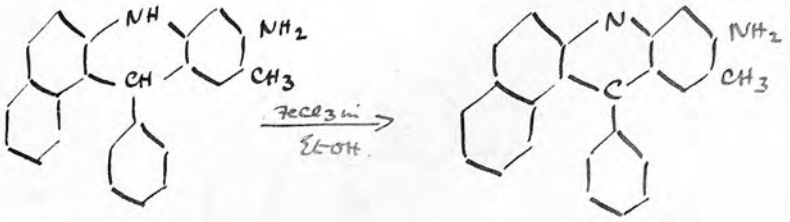
2:5-Dibromo-nitrobenzene (XXXVIII) heated with piperidine gave 2-piperidyl-5-bromo-nitrobenzene (XXXIX) which reduced gave 2-piperidyl-5-bromo-aniline (XL) and this condensed with potassium o-bromobenzoate gave 2-piperidyl-5-bromo-diphenyl-amine-6'-carboxylic acid (XLI). This on acridonation gave as main product a sulphonic acid which by analogy with the previous preparation is 1-piperidyl-4-bromo-acridone-3-sulphonic acid (XLII) with a very small quantity of a compound which has not yet been obtained perfectly pure but is most probably 1-piperidyl-4-bromo-acridone (XLIII).

While the above investigations were being made it was thought advisable to prepare some other amino-acridine derivatives and investigate the reaction of these with β-bromo-ethyl-phthalimide (with which, and its analogues, 1-amino-acridine was to be condensed as soon as it was obtained in quantity). The compounds selected for this investigation were of the type of 7-methyl-8-amino-5-phenyl-3:4-benzacridine (XLVIII), prepared by Ullmann, Rocovitza and Rozenband (Ber., 1902, 35, 316 et seq.) by the synthesis outlined below:-



(XLIV). (XLV). (XLVI)

ITHESIS
7.

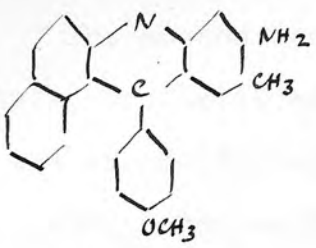


(XLVII). (XLVIII).

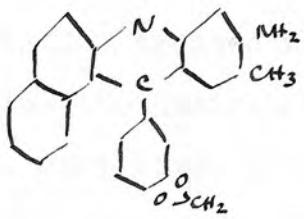
β -Naphthol, benzaldehyde, and 2:4-toluylene-diamine heated together gave the dihydro- compound which was easily oxidised by ferric chloride in alcohol to the required benzacridine.

By analogous processes the 5-(4'-methoxphenyl)- and 5-(3':4'-methylene-dioxy-phenyl)- analogues of the above benzacridine were prepared (XLIX and L respectively).

NTHESES
3 & 9.

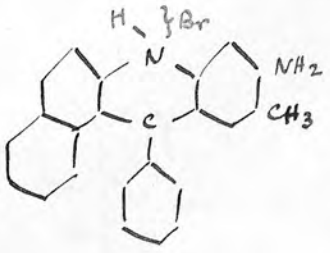


(XLIX).

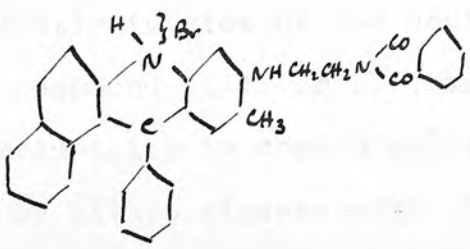


(L).

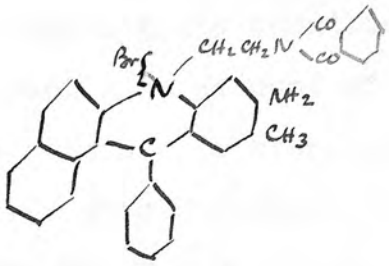
The insolubility of these benzacridines in ordinary solvents made it necessary to carry out the condensation with β-bromo-ethyl-phthalimide in nitrobenzene solution. The first of these compounds (XLVIII) heated with β-bromo-ethyl-phthalimide in this way gives a mixture which is probably composed of the hydrobromide of the original benzacridine (LI) with the hydrobromide of the desired condensation product (LII). From the mixture it has been possible to isolate by repeated crystallisation only a product which from the analysis may be the first of these two compounds which has been prepared from the original base and hydrobromic acid for comparison (mixed m.p. > 360° conveys no information).



(LI).

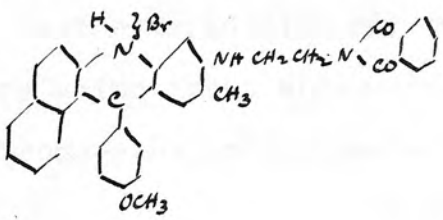


(LII A).

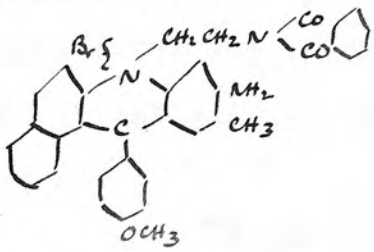


(LII B).

The second benzacridine (XLIX) treated with β-bromo-ethyl-phthalimide appears to give the desired hydrobromide of the bromo-ethyl-phthalimido- derivative (LIII), or, at any rate, a compound which analyses for that structure.



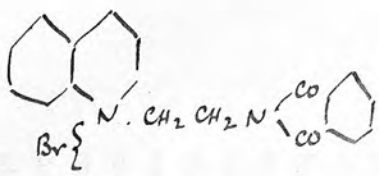
(LIII).



(LIV).

There is, of course, the other possibility that the bromo-ethyl-phthalimide may be directly attached to the tertiary nitrogen atom as in (LIV).

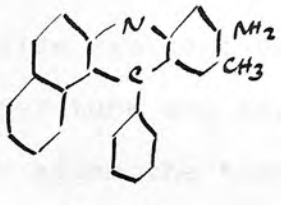
That β-bromo-ethyl-phthalimide can add to tertiary nitrogen has been proved by Seshadri (J.C.S., 1929, 2952) who heated quinoline with that reagent at 100° for 6 hr. and obtained β-phthalimido-ethyl-quinolinium bromide (LV). A repetition of this work using nitrobenzene as a solvent in the preparation gave the same compound.



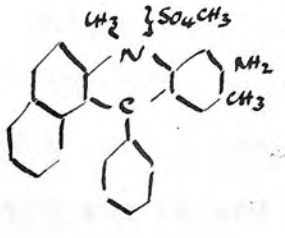
(LV).

Partly in view of the doubt regarding the constitution of the compound (LIII or LIV) and, partly on account of its insolubility in common solvents attempts to hydrolyse it, either by dilute mineral acid (HBr) or with hydrazine hydrate followed by acid (Ing and Manske, J.C.S., 1926, 2348), have not yet been made.

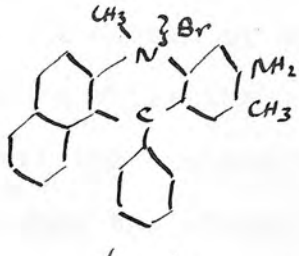
A method of overcoming the difficulty regarding the constitution of the β-phthalimido compounds can be suggested. 7-Methyl-8-amino-5-phenyl-3:4-benzacridine (XLVIII) forms a methosulphate in nitrobenzene solution which has been proved by Ullmann, Rocovitza and Rozenband (loc. cit., c.f. Hewitt, "Dyestuffs derived from Pyridine, Quinoline etc." pages 203-204) to be the acridinium methosulphate (LVI) and this contains a primary amino group which will be available for attack with β-bromo-ethyl-phthalimide.



(XLVIII).



(LVI).



(LVII).

It may be necessary to convert the methosulphate into the quaternary bromide (LVII) before acting on the compound with β-bromo-ethyl-phthalimide. The increased solubility of the acridinium salts, it is hoped, will be a decided advantage in this case.

This has had a preliminary investigation by another worker.

EXPERIMENTAL./

EXPERIMENTAL.

For convenience of discussion and reference the experimental work has been divided into a number of Syntheses.

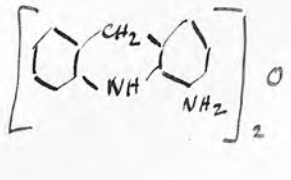
Synthesis 1.

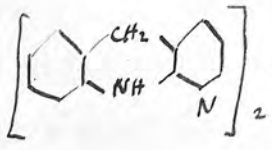
Synthesis of 1-nitro-acridone and its reduction to 1-amino-dihydroacridine followed by oxidation to 1-amino-acridine (outlined and discussed page 8). (The synthesis of 1-nitro-acridone is described in Synthesis 7, Part III, page 65).

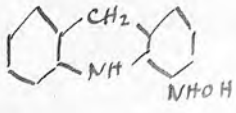
Reduction of 1-nitro-acridone.

a. In a flask fitted with a cork carrying a reflux condenser, stirrer, thermometer, leading tube for carbon dioxide and a wide tube for introducing sodium amalgam a mixture of 1-nitro-acridone (80g.), $NaHCO_3$ (380g.) and 90% alcohol (2300c.c.) was treated with 4% sodium amalgam (2550g.). A stream of carbon dioxide was kept passing through the mixture while the temperature was kept below 70°. After all the amalgam had been added the temperature was raised so that the alcohol refluxed for 1 hr. The mixture was allowed to cool to about 50°, filtered, and the dark red filtrate evaporated under reduced pressure to about 300c.c. and poured into water. The reddish precipitate so obtained was collected, dried in vacuo over H_2SO_4 and crystallised by extraction with petroleum ether. The mixture of crystals from the extraction after repeated crystallisation from petroleum ether gave bronze needles m.p. 72°. (Found: C, 77.9; H, 5.72 (Schoeller micro-combustion); N, 13.5

Required for constitution

1.  C, 76.47; H, 5.8; N, 13.7%.

2.  C, 77.2; H, 5.0; N, 13.8%.

3.  C, 73.6; H, 5.7; N, 13.4%.

Repeated attempts to obtain the results of Clemo, Perkin and Robinson have failed using either quantities given above or smaller quantities, and even with attempt to control pH value during reduction.

b. Reduction to 1-amino-acridone.

1-Nitro-acridone (10g.), 95% EtOH (100c.c.) and NH_4OH (d .880; 30c.c.) were refluxed for 5 hr. while H_2S was passed in. After standing overnight EtOH (50c.c.) and NH_4OH (d .880; 30c.c.) was added and the mixture again refluxed and treated with H_2S for 5 hr. The following day the mixture was filtered, the solid residue dried in a steam-oven and extracted twice with boiling xylene. The product (used in this state as sufficiently pure by Clemo, Perkin and Robinson loc. cit.,) was further purified by refluxing with acetic anhydride, filtering while hot, and pouring the solution into water. After boiling to decompose excess acetic anhydride the resulting mixture was filtered hot, and on cooling the filtrate crystals of the acetyl derivative separated. After collecting these, the filtrate was evaporated to small bulk and gave a further crop of crystals. After crystallising from hot water the acetyl derivative formed yellow needles m.p. 309°. Yield 6g. This acetyl derivative/

derivative was boiled with excess NaOH solution for ½ hr. and deposited an orange-yellow solid (1-amino-acridone) which washed and dried had m.p. 351°. (Clemo, Perkin and Robinson give m.p. 340°.)

Synthesis 2.

Condensation of o-chloro-benzaldehyde with o-nitro-aniline. (See page 10).

o-Nitro-aniline (7g.), o-chloro-benzaldehyde (21g.), anhydrous Na_2CO_3 (8g.), nitrobenzene (45g.) and Cu powder (0.5g.) were heated in an oil-bath at 220° for 4 hr. under reflux. The nitrobenzene was then steam-distilled till only a clear liquid was passing over. The product, which remained as a viscous mass, was heated with H_2SO_4 (d 1.84; 40c.c.) on the water-bath. The solution was diluted with a little water and some precipitated grease filtered off. The filtrate was then greatly diluted with water, boiled with charcoal, filtered and neutralised with ammonia. This yielded no large deposit (as stated by Meyer and Stein, loc. cit.,); but only a brown "milkiness". After standing to cool a small quantity of a brownish crystalline solid separated. Crystallised from MeOH this gave needles m.p. 58-60° but not in sufficient quantity for analysis. No 1-nitro-acridine m.p. 167° was obtained. (Note. Meyer and Stein do not state the yield from their experiment).

Synthesis 3. (See page 10).

Preparation of o-amino-benzaldehyde (XIX).

(c.f. Friedländer and Göhring, Ber., 17, 456).

o-Nitro-/

o-Nitro-benzaldehyde (3g.) and $FeSO_4$ (50g.) in water (500c.c.) were treated at 90-100° with excess of ammonia, adding this reagent in small quantities and shaking thoroughly after each addition. The reaction product was then steam-distilled and the distillate on cooling separated silver glancing needles which crystallised from water had m.p. 39-40° .

Condensation of o-amino-benzaldehyde and o-bromo-nitrobenzene.

o-Amino-benzaldehyde (4.84g.), o-bromo-nitrobenzene (8.08g.), Cu powder (0.5g.), anhydrous Na_2CO_3 (2.12g.) and nitrobenzene (40c.c.) were heated under reflux in an oil-bath for 3hr. The nitrobenzene was then distilled off in steam. The residue, after filtration, was heated with H_2SO_4 (d 1.84; 10c.c.) on a water-bath for 1 hr. The solution so obtained was poured on to ice, filtered, and the filtrate made alkaline with ammonia. The precipitate crystallised twice from alcohol yielded silvery shining plates of 1-nitro-acridine m.p. 166-167° . Yield only 0.5g. (Jensen and Friedrich, loc. cit., give no indication of the yield they obtained).

Synthesis 4. (See page 11 for outline).

Attempt to prepare 1-nitro-acridine from salicyl aldehyde and o-nitro-aniline.

o-Nitro-aniline (6.9g.) and salicyl aldehyde (6.1g.) were heated at 110-120° for about 10 min. and then fused zinc chloride (13.6g.) was added and the temperature raised to 150-160° for 1½ hr. With occasional stirring the mass gradually changed to a very stiff paste which solidified on cooling. The product was dissolved in alcohol and poured/

poured into an excess of ammonia solution (d .880, 250c.c., with H_2O 200c.c.). The only pure compound which could be isolated from the precipitated solid by repeated crystallisation was o-nitro-aniline.

Synthesis 5. (See page 13 for outline).

o-Piperidyl-nitrobenzene (XXXIII).

o-Chloro-nitrobenzene (20g.) and piperidine (25g.) were heated together under reflux and in a few minutes piperidine hydrochloride separated; the heating, on the water-bath, was continued for 1½ hr. and finally continued in an oil-bath at 140-150° for 1 hr. The reaction mixture was treated with water to remove excess piperidine and its hydrochloride and the aqueous solution decanted from the oily solid. This latter was dissolved in fairly concentrated hydrochloric acid and filtered to remove any traces of un-reacted o-chloro-nitrobenzene. The filtrate was diluted, made alkaline with ammonia and the orange-red piperidyl-nitrobenzene collected and dried on porous plate. Yield 25g. M.p. 78°. (Judged sufficiently pure to proceed to reduction. Lellmann and Giller, Ber., 1888, 21, 2281 give m.p. 81°).

o-Piperidyl-aniline (XXXIV).

o-Piperidyl-nitrobenzene (25g.) was dissolved in spirit (150c.c.) and conc. HCl (5c.c.), heated to boiling on the water-bath and iron filings (23g.) added in four portions at 5 min. intervals. After the final addition of the iron the mixture was kept boiling under reflux for 2 hr., made alkaline and steam-distilled. After the alcohol had passed over, the milky aqueous distillate was collected. About 2 litres of distillate carried over a colourless oil which soon/

soon solidified to a white solid, to purify which it was dried, dissolved in ether, filtered, and the ether evaporated. Colourless crystals were so obtained m.p. 45°. Yield 19g. (89% Theory). (c.f. Lellmann and Just, Ber., 1891, 24, 2103 who give m.p. 45.5°).

2-Piperidyl-diphenylamine-6'-carboxylic acid (XXXV).

o-Piperidyl-aniline (3.5g.), K o-bromobenzoate (4.8g.), amyl alcohol (10c.c.) and Cu powder (0.1g.) were heated together under reflux in an oil-bath for 3 hr. Hot water was added to the reaction product, the liquid made alkaline with caustic soda and the amyl alcohol distilled in steam. The residue was filtered from a small amount of tar and carefully neutralised by making first a little acid with dilute hydrochloric acid and then adding ammonia till neutral. The orange-yellow solid formed was collected, washed with water at the pump, and dried on porous plate. Crystallised from alcohol the acid formed brownish plates m.p. 182° (after softening at 180°). Yield 2.6g. (44% Theory). (Found: N, 9.45. $C_{18}H_{20}O_2N_2$ requires N, 9.5%).

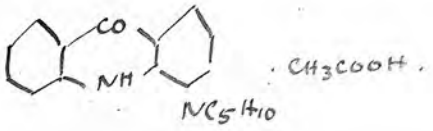
Ring Closure with 2-piperidyl-diphenylamine-6'-carboxylic acid.

Experiment 1.

2-Piperidyl-diphenylamine-6'-carboxylic acid (5g.) and H_2SO_4 (d 1.84; 35c.c.) were heated on a water-bath for 20 min. A green fluorescence developed in the solution during the heating. The liquid, after cooling, was poured into 300c.c. cold water when a creamy-white solid separated out. This was filtered, washed, mixed with warm water and made strongly alkaline/

alkaline with ammonia when most of the solid dissolved leaving a small quantity of a yellowish residue.

Residue. This, after washing, was dried in vacuo over calcium chloride. It was found insoluble in ammonia, while the original 2-piperidyl-diphenylamine-6'-carboxylic acid is very soluble in that reagent. Recrystallised from dilute acetic acid the new compound formed pale yellow plates m.p. 170°. Mixed m.p. with original carboxylic acid - all melted below 130°. (Found: C, 70.95; H, 6.6; (Schoeller micro-combustion); N, 7.9. The acetate of 1-piperidyl-acridone $C_{20}H_{22}N_2O_3$;



requires C, 71.0; H, 6.42; N, 8.2%). The yield of this fraction was small.

Filtrate.

When neutralised carefully with dilute hydrochloric acid a yellowish-white solid separated. This was filtered, washed, and dried in vacuo over calcium chloride.

Solubilities:-

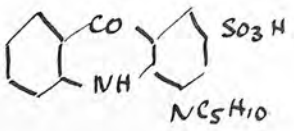
Insoluble alcohol, nitrobenzene.

Soluble concentrated hydrochloric acid, and slightly soluble in acetic acid diluted a little with water. Very soluble in cold ammonia.

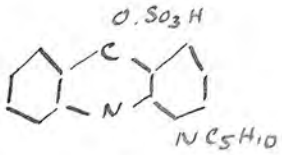
Crystallised from a large quantity of acetic acid diluted slightly with water gave yellow needles m.p. 320°. Sodium fusion of this compound indicated sulphur. (Found: N, 7.7; S, 9.4. $C_{18}H_{18}O_4N_2S$ requires N, 7.7; S, 9.0%).

Possible/

Possible structures for $C_{18}H_{18}O_4N_2S$



A.



B.

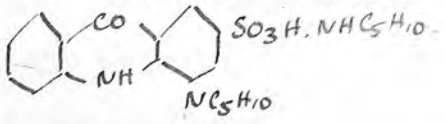
If the compound were B, the acridol sulphate, boiling with concentrated hydrochloric acid or with dilute caustic soda should split off sulphuric acid. The compound dissolved in hot concentrated hydrochloric acid but even on boiling for 3 hr., it separated again unchanged on cooling and no free SO_4 ions were found in solution. Boiled with caustic soda and filtered no sulphate was obtained in the filtrate. The structure A is, therefore, regarded as the more probable. The acid forms a piperidine salt (see below).

Experiment 2.

An attempt was made to reduce the amount of sulphonic acid formed by heating with sulphuric acid for only a short time but little difference was found in the yields. 2-Piperidyl-diphenylamine-6'-carboxylic acid (3g.) was heated with H_2SO_4 (d 1.84; 21c.c.) for 5 min. on the boiling water-bath and worked up as in Experiment 1. Yield of the acetate of 1-piperidyl-acridone -- small. Yield of 1-piperidyl-acridone-3-sulphonic acid 1.6g.

Piperidine salt of 1-piperidyl-acridone-3-sulphonic acid.
1-Piperidyl-acridone-3-sulphonic acid (1.4g.) and piperidine (3c.c.) were heated together under reflux for 5 min. when a crystalline solid was formed. This filtered and washed with benzene/

benzene had perfectly sharp m.p. 244°. (Found: N, 9.41. $C_{23}H_{29}O_4N_3S$ requires N, 9.48%).



Synthesis 6. (See page 13 for outline).

1-Piperidyl-2-nitro-5-bromobenzene (XXXVIII).

2:5-Dibromo-nitrobenzene (14g.) and piperidine (10c.c.) were heated together under reflux in a boiling water-bath. In a few minutes the contents of the flask solidified but heating was continued for ¾ hr. to complete the reaction. The reaction product was then treated with warm water to dissolve out piperidine and its hydrobromide. The oily residue was dissolved in fairly concentrated hydrochloric acid and filtered hot to remove unchanged dibromo-nitrobenzene (very little). The filtrate made alkaline with ammonia deposited an oil which did not solidify on standing (see note below). An attempt was made to get the hydrochloride crystalline by dissolving in concentrated hydrochloric acid and evaporating to small bulk. Beautiful large almost colourless crystals were so obtained. Yield 11.1g. m.p. 163° decomp. (Found: Ionisable Cl, 11.6. $C_{11}H_{14}O_2N_2ClBr$ requires ionisable Cl, 11.5%. Estimated by decomposing the hydrochloride by boiling with distilled water, filtering, and titrating the acid filtrate with standard $AgNO_3$, using Lang and Messinger's diphenylamine blue adsorption indicator method (Ber., 1930, 63, 1429)).

This/

This hydrochloride was decomposed with distilled water and, after washing the oily solid so obtained with distilled water, a solid was obtained. 1-Piperidyl-2-nitro-5-bromobenzene crystallised from light petroleum in cherry-red hexagonal plates m.p. 42°. (Note. These crystals may be used to cause the oily solid obtained on washing out the excess of piperidine and its hydrobromide from the first reaction mixture to solidify). (Found: N, 10.1. $C_{11}H_{13}O_2N_2Br$ requires N, 10.0%).

2-Piperidyl-5-bromo-aniline (XXXIX).

2:5-Dibromo-nitrobenzene (28.1g.) was treated with piperidine (20c.c.) in a boiling water-bath for 1 hr. After lixiviation with water the oily substance was seeded with a crystal of 2-piperidyl-5-bromo-nitrobenzene obtained above, and the solid so obtained was washed with water. This solid was dissolved in spirit (150c.c.) and conc. HCl (5c.c.) added and the mixture boiled under reflux on a water-bath. To the boiling mixture there was added iron filings (20g.) in four portions allowing five minutes between each addition, and the heating was continued for 2 hr. after all the iron had been added. The mixture was then made alkaline with caustic soda and filtered to remove iron oxide and the residue washed with hot alcohol.

The combined filtrate and washings was evaporated to small bulk (50-100c.c.) and allowed to stand to cool. The white plates which separated were filtered, washed on the filter with aqueous alcohol and dried on porous plate. Yield 13g. (50% Theory; but a further small portion was obtained from the mother-liquors). M.p. 67° (identical with a preparation from/

from which the compound was purified by formation of its hydrochloride, colourless needles m.p. 247° (decomp. to a blue liquid) by precipitation with HCl from alcoholic solution. This was decomposed with ammonia and the base crystallised from light petroleum). (Found: N, 11.3. $C_{11}H_{15}N_2Br$ requires N, 11.0%).

2-Piperidyl-5-bromo-diphenylamine-6'-carboxylic acid (XLI). 2-Piperidyl-5-bromo-aniline (5.1g.), K o-bromobenzoate (4.8g.) amyl alcohol (10c.c.) and Cu powder (0.1g.) were heated together under reflux in an oil-bath for 3 hr. After making alkaline with caustic soda and steam-distilling the amyl alcohol, the residue was filtered while hot and the filtrate treated with dilute hydrochloric acid till neutral when a yellow solid separated. This filtered, washed and crystallised from alcohol formed brownish-yellow plates m.p. 209-210°. Yield 3.9g. (53% Theory). (Found: N, 7.4. $C_{18}H_{19}O_2N_2Br$ requires N, 7.4%).

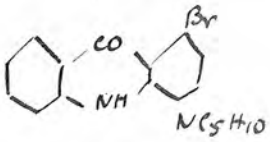
Ring Closure with 2-piperidyl-5-bromo-diphenylamine-6'-carboxylic acid.

2-Piperidyl-5-bromo-diphenylamine-6'-carboxylic acid (5g.) and H_2SO_4 (d 1.84; 35c.c.) were heated on a boiling water-bath for 15 min. during which a green fluorescence developed. The product cooled and poured into cold water (500c.c.) separated a creamy-white solid. When this mixture was made alkaline with ammonia the colour changed to a yellowish shade but the suspended solid could not be filtered. It was, therefore, made slightly acid with dilute hydrochloric acid, filtered, and the solid washed and dried in the steam-oven. The crude product had m.p. circa 225° but was evidently not one substance. This crude material contained sulphur (sodium fusion/

fusion test) which suggests presence of a sulphonic acid as in previous synthesis. Two compounds were separated from it by boiling for 2-3 min. with dilute caustic soda and filtering hot.

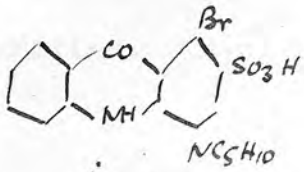
Residue insoluble in caustic soda.

Yellow in colour and only in small quantity. Readily soluble in piperidine and in alcohol. Crystallised twice from alcohol m.p. 131-132° decomp. after softening at 120°. (Found: C, 59.1; H, 4.94 (micro-combustion Schoeller). $C_{18}H_{17}ON_2Br$ requires C, 60.5; H, 4.8%), By analogy with the compound separated in the previous synthesis this substance probably has the constitution (XLIII).



(XLIII).

Filtrate. On cooling this separated beautiful lemon-yellow plates of a sodium salt. These were filtered, washed with cold water, dissolved in hot water and decomposed with dilute hydrochloric acid. The solid which separated was collected, washed thoroughly with water and dried in a steam-oven. It was found to be practically insoluble in common solvents, although slightly soluble in concentrated hydrochloric acid. It charred when heated to 250°. By analogy with the last synthesis this is probably the sulphonic acid (XLII).



(XLII).

(Found: N, 6.03; Br, 18.8. $C_{18}H_{17}O_4N_2Br$ S requires N, 6.4; Br, 18.3%).

Synthesis 7. (See page 14 for outline).

7-Methyl-8-amino-5-phenyl-3:4-benz-5:10-dihydro-acridine (XLVII).

(after Ullmann, loc. cit.)

Benzaldehyde (5.3g.) was heated with 2:4-toluylene-diamine (6.1g.) to 110° and β-naphthol (10.8g.) added and the temperature gradually raised to 180-190° when the mass changed to a yellow crystalline solid. While still warm, the mass was treated with alcohol, boiled up and filtered. This process was repeated until the insoluble residue was only feebly coloured. After drying, the solid was crystallised from aniline and had m.p. 256-260°. (Ullmann gives 271° not sharp).

7-Methyl-8-amino-5-phenyl-3:4-benz-acridine (XLVIII).

7-Methyl-8-amino-5-phenyl-3:4-benz-5:10-dihydro-acridine (8g.) was boiled with 90% alcohol (100c.c.) and brought into solution by addition of a few drops of concentrated hydrochloric acid, and to the solution ferric chloride (10g.) in 90% alcohol (50c.c.) was added immediately. The mixture was then boiled under reflux for 1 hr., cooled and poured into cold water (800c.c.). The hydrochloride separated at once; more separated overnight, and the total yield was placed in a flask with a small quantity 90% alcohol, excess ammonia added, and the mixture boiled under reflux on a water-bath for some time. The bright yellow solid so formed was collected, washed with water, dried, and crystallised from aniline. M.p. 269-271°. (Ullmann, 276°.)

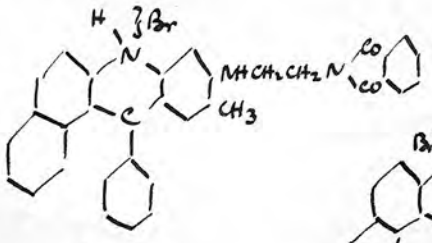
Hydrochloride/

Hydrochloride m.p. 341° decomp.

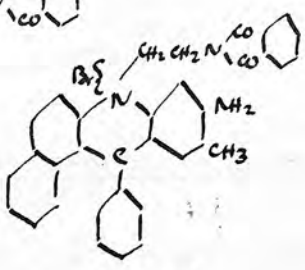
Hydrobromide m.p. 360°. (Found: Br, 18.5. $C_{24}H_{19}N_2Br$ requires Br, 19.27%).

Attempts to condense 7-methyl-8-amino-5-phenyl-3:4-benz-acridine with β-bromo-ethyl-phthalimide.

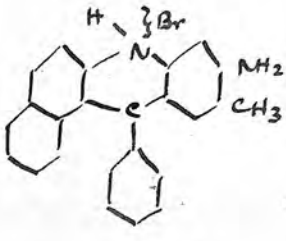
Benz-acridine (3.3g.; 1/100g.-mol.) was dissolved in nitrobenzene* (30c.c.) and β-bromo-ethyl-phthalimide (2.6g.; 1/100g.-mol.) added and the mixture gently boiled under reflux for 1 hr. On cooling, a red solid separated. This was collected, washed at the pump with warm nitrobenzene until bright red, and dried in a steam-oven. Yield 1.5g. M.p. 360°. Crystallisation was effected from nitrobenzene but no change could be observed on the melting point. This preparation was repeated many times with similar results. From the analysis table given below it is suggested that what is obtained here is a mixture of the hydrobromide of the β-bromo-ethyl-phthalimido- compound (LII A) or the compound (LII B) and the hydrobromide of the original benz-acridine (LI). Repeated crystallisations from nitrobenzene gave the sample D which is probably the compound (LI).



(LII A).



(LII B).



(LI).

$C_{34}H_{26}O_2N_3Br$/

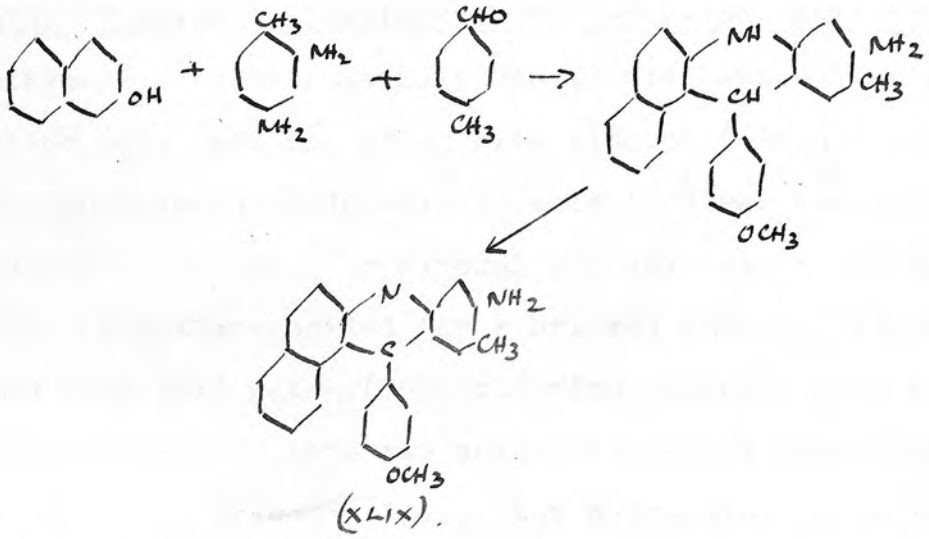
* Attempts to use ethyl or amyl alcohol as a solvent gave no reaction.

$C_{34}H_{26}O_2N_3Br$ requires N, 7.11; Br, 13.61%. $C_{24}H_{19}N_2Br$ requir
N, 6.75; Br, 19.2

	Found N.		Found Br.
1.	7.15	A. (1.	17.13
2.	6.81	(2.	17.45
3.	7.0	B. (1.	16.03
4.	7.12	(2.	16.02
5.	7.05	C. (1.	16.57
		(2.	17.1
		D. (1	18.51
		(2.	19.3

Synthesis 8.

Outline:-



(XLIX).

7-Methyl-8-amino-5-(p-methoxyphenyl)-3:4-benz-5:10-dihydro-acridine.

Anisaldehyde (6.9g.) and 2:4-toluylene-diamine (6.1g.) were heated together to 110° and β-naphthol (10.8g.) added and the temperature raised to 200-210° for ¾ hr. when the reaction mass solidified. Boiled with alcohol and filtered this gave a yellow solid (12-14g.) which crystallised from aniline gave yellow/

yellow rectangular needles (9g.) m.p. 228-229°. A nitrogen estimation (7.14%) indicated that the composition was certainly close to the required acridine but the melting point was surprisingly low.

Fractional crystallisation from aniline gave first a white solid (6g. M.p. 255-260°) and from the mother-liquors a smaller quantity of a bright yellow solid (m.p. 287-290°.)

The white solid was further purified by crystallisation from acetone slightly diluted with water when pure white needles were obtained m.p. 253°. This is the dihydro-benzacridine. (Found: N, 7.4 $C_{25}H_{22}ON_2$ requires N, 7.65%). On oxidation it gives the benzacridine by loss of two hydrogen atoms.

The bright yellow solid crystallised from alcohol gave yellow needles m.p. 294°; identical with the benzacridine described below.

7-Methyl-8-amino-5-(p-methoxyphenyl)-3:4-benz-acridine (XLIX).

7-Methyl-8-amino-5-(p-methoxyphenyl)-3:4-benz-5:10-dihydro-acridine (4g.) was boiled up with alcohol (50c.c.) and a few drops concentrated hydrochloric acid to clear the solution. Ferric chloride (5g.) in alcohol (30c.c.) was added immediately and the mixture boiled for ½ hr. and then cooled and poured into cold water (500c.c.) with stirring when a red solid separated. This was collected at the pump, washed with water and dried. 3g. of the hydrochloride of the benzacridine so collected was treated with alcohol and excess of ammonia. The mixture was warmed to complete the decomposition, diluted with water, filtered, and washed with water. After drying and crystallising from aniline or nitrobenzene yellow needles m.p. 294° were obtained.

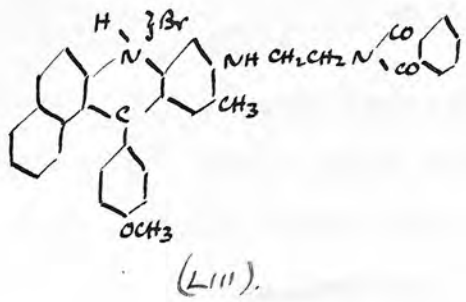
Note. In the preparation of the benzacridine there is no necessity/

necessity to isolate the dihydro-compound as was done above. The crude dihydro-compound may be oxidised with ferric chloride. From the same quantities of anisaldehyde etc., working in this manner 9g. of the 7-methyl-8-amino-5-(p-methoxyphenyl)-3:4-benz-acridine were obtained.

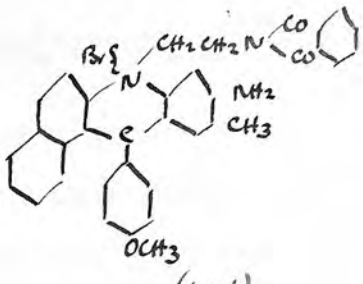
Hydrobromide. Precipitated from alcohol with HBr and crystallised from nitrobenzene, m.p. 294°. (Found: Br, 18.3 $C_{25}H_{21}ON_2Br$ requires Br, 18.4%).

Attempts to condense β-bromo-ethyl-phthalimide with 7-methyl-8-amino-5-(p-methoxyphenyl)-3:4-benz-acridine.

Benzacridine (3.6g.), β-bromo-ethyl-phthalimide (2.54g.) and nitrobenzene (10c.c.) were heated under reflux so that the nitrobenzene just boiled. After 2 hr. the reaction mixture was allowed to cool and the red needles which crystallised were collected and recrystallised from nitrobenzene. M.p. 297-298°. Yield 2.9g. From the analytical data and evidence from mixed melting points given below this is most probably the desired condensation compound but may have constitution (LIII) or (LIV).



(LIII).



(LIV).

Analysis. (Found: Br, 12.89; 13.3; 13.08; N, 7.5 $C_{35}H_{28}O_3N_3Br$ requires Br, 12.94; N, 6.8%).

Melting Point data.

		M.p.
1.	7-Methyl-8-amino-5-(p-methoxyphenyl)-3:4-benz-acridine	294°

2./

2. 7-Methyl-8-amino-5-(p-methoxyphenyl), 3:4-benz-acridine hydrobromide 294°

3. β-Bromo-ethyl-phthalimido- derivative of 1. 297-298°

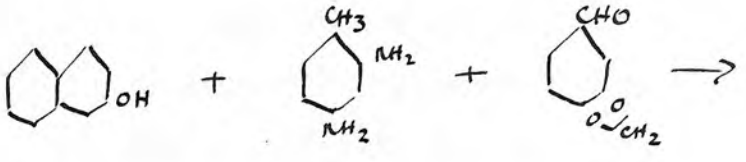
4. 3 decomposed with ammonia and the yellow compound obtained crystallised from nitrobenzene 287°

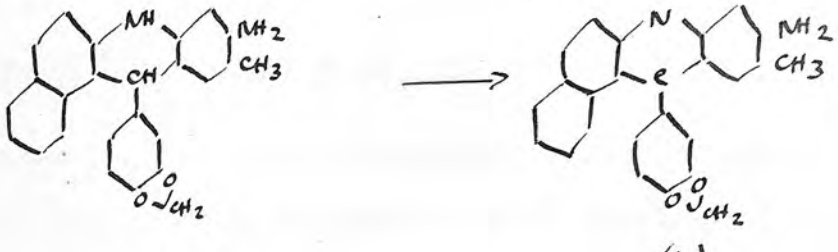
Mixed m.p. 2 and 3 291°.

" 1 and 4 290°.

Synthesis 9.

Outline:-





(1).

7-Methyl-8-amino-5-(3':4'-methylenedioxyphenyl)-3:4-benz-5:10-dihydro-acridine.

Piperonal (7.5g.) and 2:4-toluylene-diamine (6.1g.) were heated to 120° for a short time and then β-naphthol (10.8g.) was added and the temperature raised to 200° for ¾ hr. While still hot the mass was treated with alcohol (100c.c.) and boiled under reflux. After filtration, the residue was twice boiled with alcohol as above. The insoluble residue from this treatment was dissolved in aniline, allowed to crystallise, filtered at the pump and washed with spirit when white rectangular needle-shaped crystals were obtained, m.p. 274°. Yield 3g. (Found: C, 78.3; H, 5.54; N, 7.35 $C_{25}H_{20}O_2N_2$/

$C_{25}H_{20}O_2N_2$ requires C, 78.9; H, 5.30; N, 7.37%).

7-Methyl-8-amino-5-(3':4'-methylenedioxyphenyl)-3:4-benzacridine (L).

The dihydro- compound (above) (2g.) was boiled with alcohol (30c.c.) and a few drops concentrated hydrochloric acid added to clear the solution. Ferric chloride (4g.) in alcohol (20c.c.) was added immediately and the mixture boiled for ½ hr. under reflux. On pouring into cold water (600c.c.) the hydrochloride of the base separated and after filtration this was heated with a small quantity of alcohol and excess of ammonia. The yellow solid which separated was dried and crystallised from aniline and then formed yellow needles m.p. 293°. (Found: N, 7.6. $C_{25}H_{18}O_2N_2$ requires N, 7.4%).

Synthesis 10. (See page 16).

Quinoline (2.6g.) and β-bromo-ethyl-phthalimide (5.0g.) heated under reflux in nitrobenzene solution for a short time (5-10 min.) and allowed to cool deposited a crystalline solid which was filtered and dried in a steam-oven till free from nitrobenzene. This solid was found to be identical with β-phthalimido-ethyl-quinolinium bromide (LV) m.p. 264°. Yield 3g.

P A R T II.

NITRATION of HALOGENATED ANILINES and ACETANILIDES.

For work described later in this Thesis (page 48) it was necessary to develop a clean and quick method of preparing nitro-halogenated anilines and acetanilides. The early work of Nölting and Collin (Ber., 20, 1379) and the modification of Chattaway, Orton and Evans (Ber., 33, 3062) for the nitration of o-chloro-aniline was examined and found to give very poor yields. The reduction of 2:4-dinitro-chlorobenzene with tin and hydrochloric acid gave no better (Claus and Stiebel, Ber., 20, 1379). From a review of Lobry de Bruyn's work on this subject (Rec. trav. chim., 1916, 36, 126 et seq.) it was thought possible that nitration of o-chloro-aniline in sulphuric acid solution with potassium nitrate might prove successful and it was found that, if the aniline and the nitrate were separately dissolved in concentrated sulphuric acid and cooled to 0° C. before mixing and kept about that temperature during the reaction, good yields of 5-nitro-2-chloro-aniline were obtainable. The method in this case is really a modification of that of Chattaway, Orton and Evans (loc. cit.) and that used by Lobry de Bruyn (Rec. trav. chim., loc. cit., 115) and Fourneau, Tréfouel and Wancolle (Bull. Soc. Chim., 1930, 47, 738) in that potassium nitrate in sulphuric acid is used instead of nitric acid, d 1.5, in sulphuric acid, and further, after nitration and pouring on to ice neutralisation with ammonia is avoided by diluting sufficiently with/

with water to hydrolyse the sulphate which is presumably formed. The yield in this particular case is smaller than that claimed by Fourneau probably due to the solubility of 5-nitro-2-chloro-aniline in water.

The method was found to give excellent results in the case of o-bromo-aniline, and of p-chloro- and p-bromo-acetanilide.

TABLE 1.

Compound nitrated.	Compound obtained.	Yield.	M.p.
o-chloro-aniline	5-nitro-2-chloro-aniline	52-58%	117°.
o-bromo-aniline	5-nitro-2-bromo-aniline	70%	138°.
p-chloro-acetanilide	2-nitro-4-chloro-acetanilide	66%	103°.
p-bromo-acetanilide	2-nitro-4-bromo-acetanilide	74%	104°.

In the nitration of p-bromo-acetanilide by this method no anomalous results such as those obtained by Griffith (J.C.S., 1924, 940) were obtained. This worker showed that p-bromo-acetanilide when nitrated with excess of nitric acid, d, 1.5, at 10° C. so as to yield 2-nitro-4-bromo-acetanilide (Remmers, Ber., 1874, 7, 347) and then the solution of the latter in the excess of nitric acid treated further with sulphuric acid gave a mixture of 2:4-dibromo-6-nitro-, 4-bromo-2-nitro-, and 4-bromo-2:6-dinitro-acetanilides.

In contrast, when nitrated with twice the theoretical quantity of potassium nitrate under conditions mentioned above practically the same yield of the mono-nitro compound was obtained.

2-nitro-4-chloro-acetanilide and 2-nitro-4-bromo-acetanilide may be deacetylated to give the corresponding anilines by boiling with 2% aqueous caustic soda (c.f. Lobry de Bruyn/

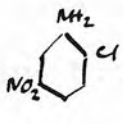
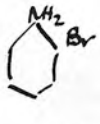
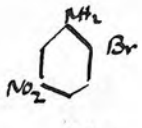
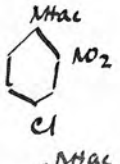
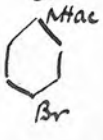
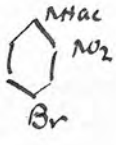
Bruyn, loc. cit., 133).

In the nitration of p-chloro-aniline neutralisation of the diluted reaction product with ammonia was found necessary and the yield of 3-nitro-4-chloro-aniline was 50-58% (c.f. Lobry de Bruyn, loc. cit., 153).

Nitration of p-iodo-acetanilide by this method proved unsuccessful due to the liberation of iodine by the nitric-sulphuric acid solution.

It is interesting to note in passing that the results of the above experiments confirm, though not with the same degree of accuracy as the work of de Bruyn, the position taken up by the nitro-group when o-halogenated anilines and p-halogenated acetanilides are nitrated in sulphuric acid solution. This is summarised in Table 11.

TABLE 11.

Compound nitrated.	Compound obtained.	Percentage Yield. de Bruyn	Percentage Yield. Nisbet.
		100	52-58
			70
		100	66
			74

E X P E R I M E N T A L.

The o-chloro-, o-bromo-, and p-chloro-anilines used in this/

this work were prepared from the corresponding halogenated nitro-benzenes by reduction by West's method (J.C.S., 1925, 494).

Preparation of o-chloro-aniline.

o-chloro-nitrobenzene (60g.) was heated to boiling on a water-bath with spirit (250c.c.) and HCl, d, 1.12, (5c.c.). Iron filings (70g.) were added in four portions, five minutes being allowed between each addition. The mixture was kept at vigorous ebullition and heating continued for two hours after the final addition of the iron. The mixture was then made alkaline with caustic soda and steam distilled. Alcohol distilled over first and when the distillate turned milky this portion was collected separately. The chloro-aniline was extracted from this with ether, dried over potassium carbonate, and distilled. The fraction b.p. 205-209°C. was collected. Yield 40g. (82% Theory).

Preparation of o-bromo-aniline.

Following the same method from 36g. o-bromo-nitrobenzene 24g. (78% Theory) o-bromo-aniline b.p. 144-146°C. at 13mm. was obtained.

Preparation of p-chloro-aniline.

From p-chloro-nitrobenzene (60g.) p-chloro-aniline m.p. 71°C. (39g. 80% Theory) was obtained pure from the first steam distillation during which it crystallised in the condenser.

In all the following nitrations H_2SO_4, d, 1.84, was used for solution of the halogenated aniline or acetanilide and KNO_3.

Nitration of o-chloro-aniline.

o-Chloro-aniline (12.7g.) was dissolved in H_2SO_4 (100c.c.); KNO_3/

KNO_3 (10.2g.) was dissolved in H_2SO_4 (100c.c.); and the two solutions cooled to 0°C. in ice and salt. The nitrate solution was added to the first solution during ½ hr. the temperature being kept below 2°C. The reaction mixture was poured on to ice (300g.) (white solid separated) and then into 4 litres of water when a yellow crystalline solid separated. This was filtered, washed with cold water to neutrality, dried, and crystallised from 100c.c. spirit. Yield 10g. (58% Theory) of 5-nitro-2-chloroaniline m.p. 117°.

Nitration of o-bromo-aniline.

o-bromo-aniline (8.6g.) in H_2SO_4 (80c.c.) and KNO_3 (5.05g.) in H_2SO_4 (100c.c.) were cooled and mixed as above. The 5-nitro-2-bromo-aniline separated from 4 litres water in flocks of yellow needles. The unrecrystallised compound was dried in a steam-oven and had m.p. 136-137°. (almost pure). Yield 9.0g. (83% Theory). Recrystallised from spirit 5-nitro-2-bromo-aniline formed long orange yellow needles m.p. 138°. Yield 7.5g. (70% Theory). (Found: Br, 37.12. $C_6H_5O_2N_2Br$ requires Br, 36.86%).

Nitration of p-chloroacetanilide.

p-Chloro-acetanilide (5g.) in H_2SO_4 (100c.c.) and KNO_3 (3.5g.) in H_2SO_4 (50c.c.) were cooled and mixed as above. After the addition the reaction mixture was allowed to stand ½ hr. before pouring on to crushed ice and diluting to 4l. with water. The yellow solid which separated was filtered, washed till neutral and crystallised from 50% alcohol. The 3-nitro-4-chloroacetanilide formed yellow needles m.p. 103°. Yield 4.2g. (66% Theory).

Nitration of p-bromoacetanilide.

p-/

p-Bromoacetanilide was prepared by the method of Remmers, (Ber., 1874, 7, 346).

Nitration. p-Bromoacetanilide (5g.) in H_2SO_4 (100c.c.) and KNO_3 (2.5g.) in H_2SO_4 (100c.c.) were cooled and mixed as above and stood for 15 min. to complete the reaction. The resulting yellow-brown solution was poured on to crushed ice, diluted to 4l. with water; the solid filtered, washed to neutrality and dried. Crystallised from 50% alcohol 2-nitro-4-bromoacetanilide formed yellow needles m.p. 104°. Yield 4.5g. (74% Theory). Nitration with KNO_3 (5g. i.e. twice theoretical quantity for mono-nitration) and worked up as above gave again 4.5g. of 2-nitro-4-bromoacetanilide m.p. 104°.

Hydrolysis of 2-nitro-4-bromoacetanilide.

2-Nitro-4-bromoacetanilide (3g.) was heated with 2% aqueous NaOH (150c.c.) under reflux for 20 min. and cooled. The reddish solid which separated was crystallised from diluted alcohol and formed reddish-yellow needles m.p. 110-112°. (c.f. hydrolysis of 2-nitro-4-chloroacetanilide by Lobry de Bruyn loc. cit., 133).

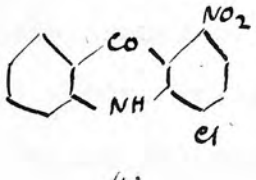
Nitration of p-chloroaniline.

p-Chloroaniline (12.7g.) in H_2SO_4 (100c.c.) and KNO_3 (10.2g.) in H_2SO_4 (100c.c.) were cooled and mixed as above. The reaction mixture was poured on to ice (300g.) and then into water (4l.) when a small amount of a dark-brown solid separated. More of this settled out on adding a small quantity of ammonia and was filtered off before making the liquid slightly alkaline with this reagent. At this stage an orange-yellow solid separated, and after crystallisation from boiling water gave orange-yellow needles m.p. 102-103°. (Yield 8.5-10g. 50-58% Theory).

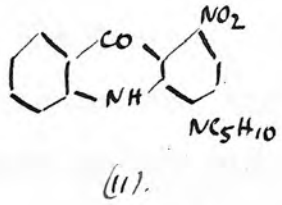
P A R T III.

THE REACTIVITY of GROUPS in SUBSTITUTED ACRIDONES.

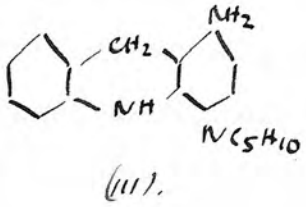
In the search for methods of preparing 1-amino- and 1-alkyl-amino-acridines and related compounds referred to in the Introduction and Part 1 the possibility of replacing halogen in the 1-position in acridones by piperidine has been investigated. It was hoped, for example, that 1-chloro-4-nitro-acridone (I) would be converted into 1-piperidyl-4-nitro-acridone (II) which on reduction would give the corresponding piperidyl-amino-dihydro-acridine (III) or piperidyl-amino-acridine (IV).



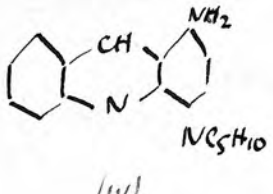
(I).



(II).



(III).



(IV).

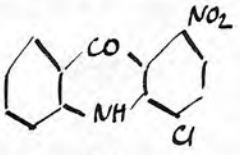
It was found, however, that piperidine acting on (1) replaced not the halogen atom, but the nitro group in position 4. An extension of the work by a research student showed that piperazine also removed the nitro group.

Now, numerous cases are known in which one of two cationoid groups in an aromatic nucleus, ortho or para to one another/

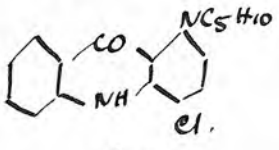
another, is replaced by an anionoid reagent. Thus, o- and p-dinitro-benzenes on heating with potash are converted into the corresponding nitrophenols, and 4-chloro-1:2-dinitrobenzene heated with sodium methylate has the 2-nitro group replaced (ter Weel, Rec. trav. chim., 1916, 35, 44).

It is also known that the carbonyl group in anthraquinone acts as a cationoid group from the facts that 1-chloro-anthraquinone gives 1-piperidyl-anthraquinone when heated with piperidine (D.R.-P. 136777), the nitro group in 1-nitro-anthraquinone may be replaced by the methylamino- (D.R.-P. 144634), dimethylamino-, or piperidyl- group (D.R.-P. 136777), and in 4-chloro-1-nitro-anthraquinone both the nitro group and the chlorine atom are replaced on heating with p-toluidine (D.R.-P. 126803).

It was recognised, therefore, that in the nitro-chloro-acridone (I) there is a heterogeneous polarity caused by the two cationoid groups ortho to one another (CO and NO_2) so that the p-nitro group, instead of activating the halogen atom and facilitating its replacement by the negative reagent, is itself replaced, the product being (V).

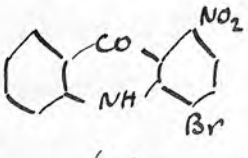


(I)

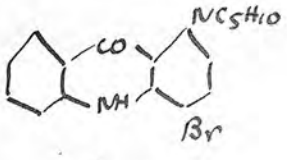


(V).

1-Bromo-4-nitro-acridone (VI) by the same reaction gives 1-bromo-4-piperidyl-acridone (VII).



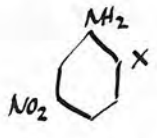
(VI).



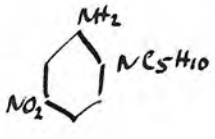
(VII).

Further/

Further, that the removal of the heterogeneous polarity proceeds more readily than the replacement of activated halogen may be inferred, since such reaction takes place in this case, whereas in 2-halogeno-5-nitro-anilines (VIII), in the absence of heterogeneous polarity, the removal of halogen by piperidine to give 5-nitro-2-piperidyl-aniline (IX) proceeds normally on heating in a sealed tube *

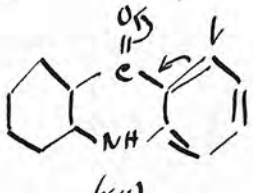


(VIII; X = Cl or Br).

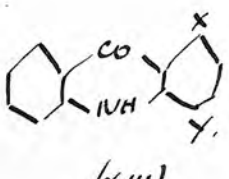


(IX).

The carbonyl group in acridones, then, is definitely cationoid and as such makes the carbon atom in position 4 susceptible to attack by anionoid reagents (electronic explanation XII; the arrow indicates the point of attack by anionoid reagents). Halogen atoms attached to this carbon atom should, therefore, be easily replaced by groups such as piperidyl.

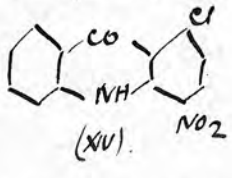


(XII).

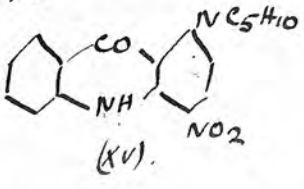


(XIII).

It has been found that 1:4-dihalogeno-acridones (XIII, X and Y = Halogen) have the halogen X removed to give compounds identical with (V) and (VII) in much better yield than by the removal of the nitro group from (I) and (VI). 1-Nitro-4-chloro-acridone (XIV) has the chlorine atom removed to give 1-nitro-4-piperidyl-acridone (XV).



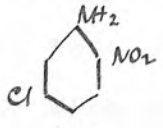
(XIV).



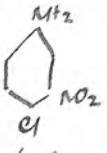
(XV).

* The action of piperidine on 2-nitro-5-chloro-aniline (X) and/

and 3-nitro-4-chloro-aniline (XI) under various conditions has been investigated but no pure reaction products have been obtained.

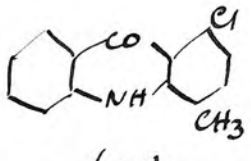


(X)



(XI)

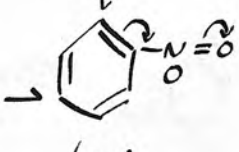
1-Methyl-4-chloro-acridone (XVI) is unchanged even on heating for a long time with piperidine.



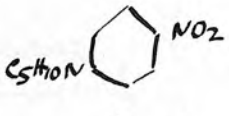
(XVI)

This is in agreement with the effect of a methyl group on substitution and replacement in the benzene ring i.e. facilitating cationoid attack and retarding anionoid attack.

Bradley and Robinson (J.C.S., 1932, 1255) have shown that even hydrogen may be replaced by piperidyl in such compounds as nitrobenzene (XVII) yielding p-piperidyl-nitrobenzene (XVIII).

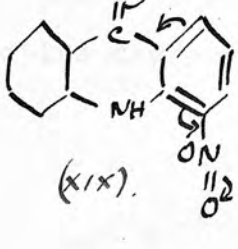


(XVII).

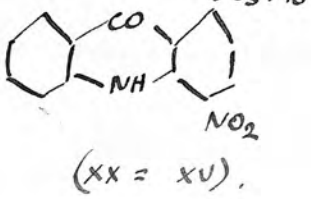


(XVIII).

The somewhat similar case of 1-nitro-acridone where the cationoid effects of nitro and carbonyl groups will be cumulative (XIX)



(XIX).

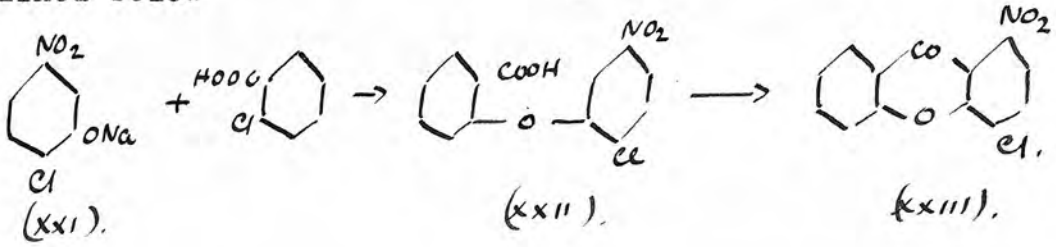


(XX = XV).

might/

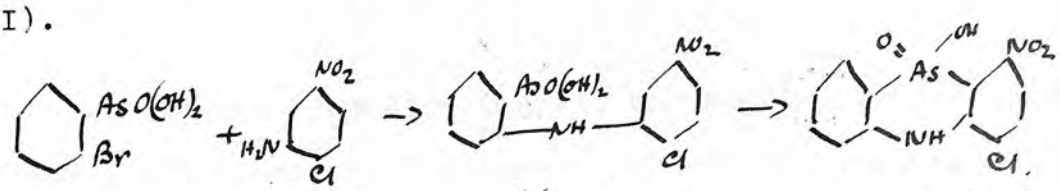
might be expected to give (XX); but no such reaction took place on heating with excess of piperidine in the presence of sodamide. The insolubility of 1-nitro-acridone may have something to do with the failure of this reaction.

The cationoid character exhibited at the carbon atom ortho to the carbonyl group in anthraquinones and acridones should also be exhibited in such compounds as the xanthones and phenarsazinic acids. Preliminary experiments have been undertaken in the preparation of 2-chloro-5-nitro-phenol by diazotisation of 2-chloro-5-nitro-aniline so that it may be used in the synthesis of 4-nitro-1-chloro-xanthone (XXIII) outlined below



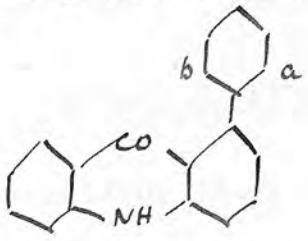
(XXI). (XXII). (XXIII).

and in the preparation of o-bromo-phenylarsinic acid so that it may be used in the synthesis of the arsenic compound (XXVI).



(XXIV). (XXV). (XXVI).

Further, now that halogen in position 4 in acridones is known to be reactive, it should be possible to synthesise compounds of the type (A) which from their analogy to optically active diphenyl derivatives should be resolvable.

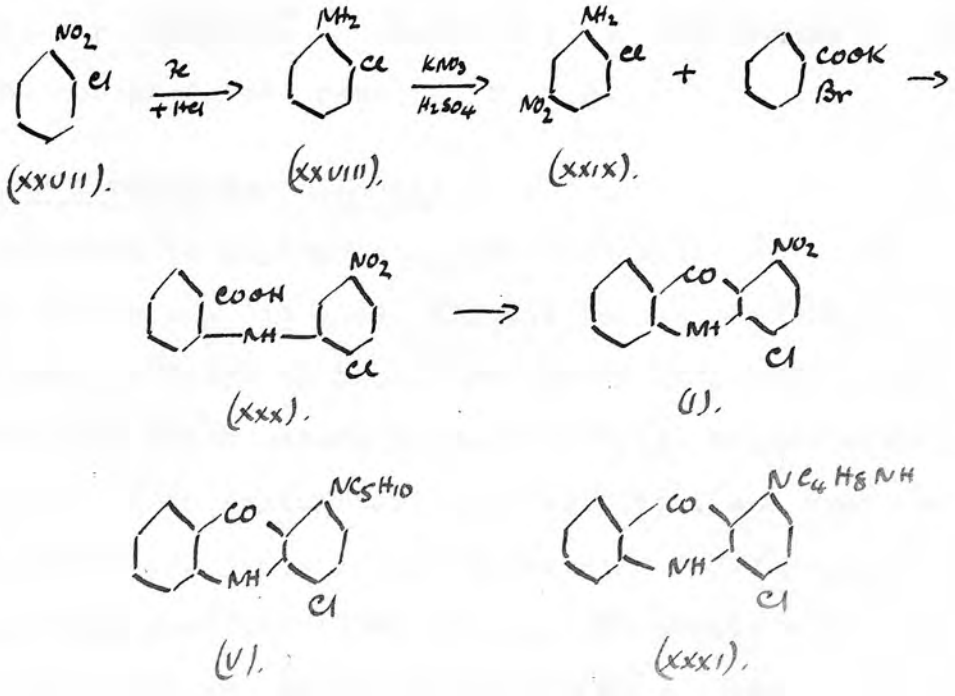


(A).

EXPERIMENTAL.

For convenience of discussion and reference the experimental work has been divided into a number of syntheses each of which is given in outline before the description of the preparations involved.

Synthesis 1.



o-Chloro-nitrobenzene (XXVII) was reduced to o-chloro-aniline (XXVIII) and this nitrated to 5-nitro-2-chloro-aniline (as described in Part II, pages 40-41). Condensation of this with the potassium salt of o-bromo-benzoic acid gave the diphenylamine-carboxylic acid (XXX) which was acridonated with sulphuric acid, and the nitro-chloro-acridone (I) on treatment with piperidine or piperazine gave the piperidyl- or piperazyl-acridone (V) and (XXXI) respectively.

Preparation of 2-chloro-5-nitro- diphenylamine-6'-carboxylic acid (XXX).

5-Nitro-2-chloroaniline (3.4g.), K o-bromobenzoate (4.8g.), amyl/

amyl alcohol (10c.c.), and Cu powder (0.1g.) were refluxed in an oil-bath for 4 hr. The reaction mixture was made alkaline with NaOH, the amyl alcohol distilled in steam, the residue cooled, and the filtered solution made acid with dilute HCl when a yellow solid separated. After filtration and washing this was dried in the steam-oven and crystallised from glacial acetic acid when the carboxylic acid formed golden-yellow needles m.p. 260-261°. Yield 2.3g. (40% Theory). (Found: N, 9.8. $C_{13}H_9O_4N_2Cl$ requires N, 9.6%).

1-Chloro-4-nitro-acridone (I).

2-Chloro-5-nitro-diphenylamine-6'-carboxylic acid (5g.) was heated with H_2SO_4, (d 1.84, 35c.c.) for 15 min. on the boiling water-bath, allowed to cool, and poured into cold water. The yellow solid which separated was filtered, boiled with water, then with dilute sodium carbonate solution, and again with water, filtered, dried in the steam-oven and crystallised from a large quantity (500c.c.) glacial acetic acid. The acridone formed yellow needles m.p. 320°. Yield 3g. (64% Theory). (Found: N, 10.0. $C_{13}H_7O_3N_2Cl$ requires N, 10.2%).

1-Chloro-4-piperidyl-acridone (V).

1-Chloro-4-nitro-acridone (1.5g.) was refluxed with piperidine (7c.c.) until all the solid went into solution. The resulting deep red liquid was poured into water, the precipitated solid filtered, and crystallised from dilute alcohol. The piperidyl compound formed beautiful yellow needles m.p. 110°. Yield 0.6g. (43% Theory). (Found: N, 8.9; Cl, 11.1. $C_{18}H_{17}ON_2Cl$ requires N, 9.0; Cl, 11.3%). The hydrochloride of this base was prepared by dissolving the base in chloroform

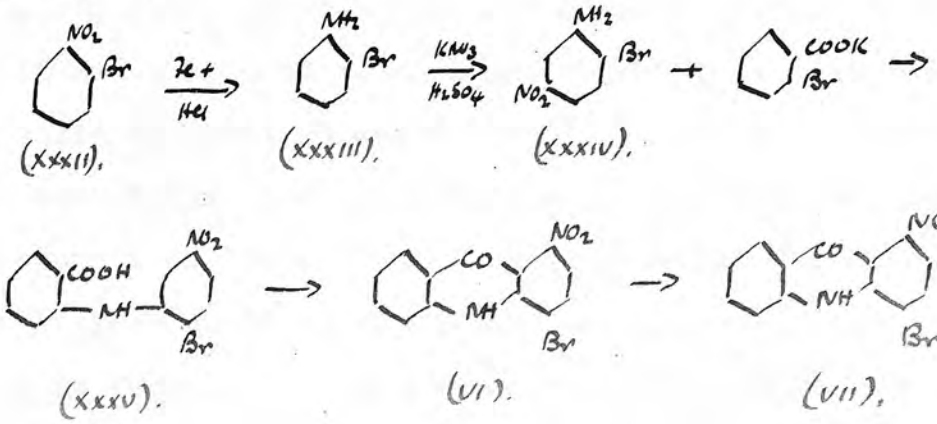
and/

and passing in dry HCl gas. When crystallised from water it formed yellow needles m.p. 168-169°.

1-Chloro-4-piperazyl-acridone (XXXI).

1-Chloro-4-nitro-acridone (1.4g.) and piperazine (3.3g.) were refluxed till homogeneous, poured into water and the precipitated solid crystallised from dilute alcohol formed brownish-yellow needles m.p. 197-198°. Yield 0.9g. (Found: N, 13.8; Cl, 10.3. $C_{17}H_{16}ON_3Cl$ requires N, 13.4; Cl, 11.3%).

Synthesis 2.



o-Bromo-nitro-benzene was reduced to o-bromo-aniline and this nitrated to 5-nitro-2-bromo-aniline (see Part II, pages 40 and 41). Potassium o-bromo-benzoate condensed with this gave 2-bromo-5-nitro-diphenylamine-6'-carboxylic acid (XXXV) which treated with sulphuric acid lost water to give the acridone (VI). This heated with piperidine lost its nitro group to give the piperidyl-bromo-acridone (VII).

2-Bromo-5-nitro-diphenylamine-6'-carboxylic acid (XXXV).

5-Nitro-2-bromo-aniline (4.35g.), K o-bromo-benzoate (4.8g.) amyl alcohol (10c.c.), and Cu powder (0.1g.) were refluxed in an oil-bath for 4 hr. The reaction product was made alkaline with/

with NaOH, the amyl alcohol distilled in steam, the residue cooled, filtered from some unchanged 5-nitro-2-bromo-aniline, and the filtrate made acid with dilute HCl. The yellow solid which separated was filtered, washed with water and dried in the steam-oven. Crystallised from glacial acetic acid the diphenylamine-carboxylic acid formed yellow needles m.p. 252°. Yield 2.3g. (34% Theory). (Found: Br, 24.2. $C_{13}H_9O_4N_2Br$ requires Br, 23.7%).

1-Bromo-4-nitro-acridone (VI).

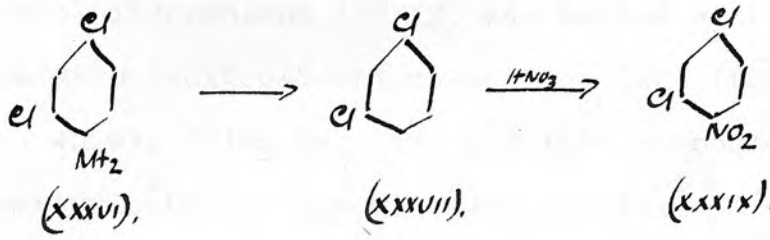
2-Bromo-5-nitro-diphenylamine-6'-carboxylic acid (4g.) and H_2SO_4, (d 1.84; 28c.c.) were heated on a boiling water-bath for 15 min., allowed to cool and poured into cold water. The solid so obtained was filtered, boiled with water, then with dilute sodium carbonate solution, and again with water and finally dried in a steam-oven and crystallised from a large quantity of glacial acetic acid. The acridone formed pale lemon-coloured microcrystalline needles m.p. 305°. Yield 2.1g. (55% Theory). (Found: Br, 24.9. $C_{13}H_7O_3N_2Br$ requires Br, 25.1%).

1-Bromo-4-piperidyl-acridone (VII).

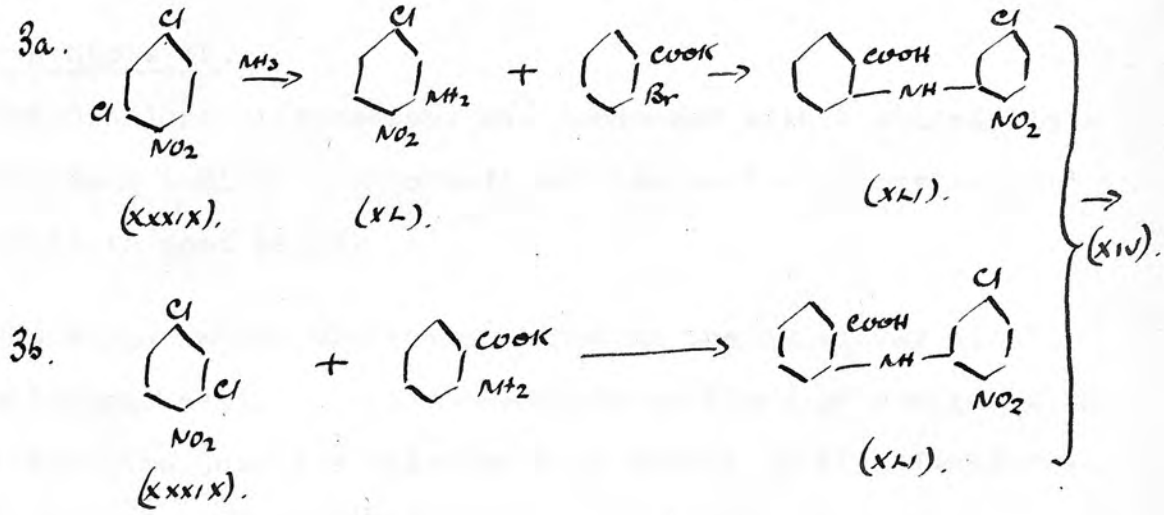
1-Bromo-4-nitro-acridone (1.8g.) and piperidine (7c.c.) were mixed when a deep red colour developed. The mixture was boiled under reflux for 1¼ hr. The solid gradually dissolved (more rapidly during the second half of the period) to a dark red liquid which on pouring into water gave a bright yellow solid. This filtered, washed with water, and crystallised from dilute alcohol gave beautiful needles, softening at 98-102° and m.p. 112° decomp. Yield 1.5g. (74% Theory). (Found: Br, 21.6. $C_{18}H_{17}ON_2Br$ requires Br, 22.4%)./

Br, 22.4%). This compound dissolved in chloroform and treated with HCl gas gave a hydrochloride which crystallised from water in pale yellow matted needles m.p. 164-165°.

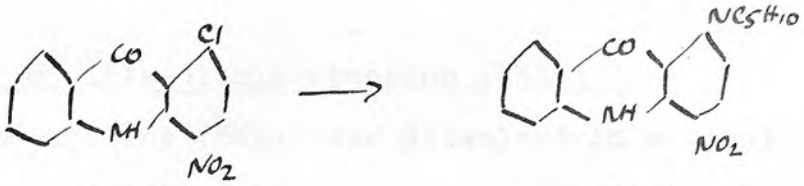
Synthesis 3.



(XXXVI). (XXXVII). (XXXIX).



(XXXIX). (XL). (XLI). (XLI). (XIV).



(XIV). (XV).

2:4-Dichloro-aniline (XXXVI) was diazotised and the diazonium compound boiled with alcohol to give meta-dichlorobenzene (XXXVII) according to the directions of Chattaway and Evans (J.C.S., 1896, 850) with the modifications of Hollemann (Rec. trav. chim., 1904, 23, 359). The meta-dichlorobenzene was then nitrated according to the method of Reiding (Rec. trav. chim., 1904, 23, 369) to give 2:4-dichloro-nitrobenzene (XXXIX)/

(XXXIX). From this point two methods were available for the synthesis of 2-nitro-5-chloro-diphenylamine-6'-carboxylic acid (XLI).

Synthesis 3a.

2:4-dichloro-nitrobenzene (XXXIX) was heated with alcoholic ammonia to give 1-nitro-5-chloro-aniline (XL) (Lobry de Bruyn, Rec. trav. chim., 1916, 36, 148) and this compound condensed with potassium o-bromo-benzoate gave the desired diphenylamine-6'-carboxylic acid. This gave rather a poor yield.

Synthesis 3b.

2:4-Dichloro-nitrobenzene was condensed with K anthranilate and gave 2-nitro-5-chloro-diphenylamine-6'-carboxylic acid (XLI) in good yield.

The acridonation was accomplished in the usual way with sulphuric acid. 1-Nitro-4-chloro-acridone on heating with piperidine lost its chlorine atom easily to give 1-nitro-4-piperidyl-acridone (XV).

Preparation of meta-dichlorobenzene (XXXVII).

2:4-Dichloro-aniline (54g.) was dissolved in alcohol (320c.c.) and concentrated HCl (108c.c.) added. The hydrochloride separated on addition of the HCl. To the mixture a suspension of KNO_2 (25g.) in alcohol was added and the reaction mixture allowed to stand for 2 hr. during which time nitrogen was slowly given off. After boiling under reflux for $\frac{1}{2}$ hr. the mixture was allowed to stand over-night and steam-distilled the following day. The alcohol which passed over first was collected and diluted with slightly more than its own volume of water. The oil which settled out/

out was separated, dried over $CaCl_2$, and distilled, and gave a colourless oil b.p. 169-171°. (Literature 172° corr.). (Yield 21g.).

2:4-Dichloro-nitrobenzene (XXXIX).

m-Dichloro-benzene (20g.) was added slowly to nitric acid (d 1.505, 67c.c.) cooled in ice. The reaction appeared to be very slow and after 3 hr. intermittent shaking (cooled in ice all the time) the flask was removed from the ice-bath and allowed to stand at room temperature with occasional shaking. After about 1½ hr. the contents of the flask became homogeneous and the solution was poured into cold water when a greenish-white oil separated. After pouring off the acid liquor and covering the oil with fresh water it solidified to a greenish-white solid which dried on porous plate had m.p. 30-31°. (Reiding, loc. cit., and de Bruyn, Rec. trav. chim., 1916, 36, 148, give m.p. 31.5-32°). Yield 21g. This was judged sufficiently pure for further work.

2-Nitro-5-chloro-aniline (XL).

2:4-Dichloro-nitrobenzene (in quantities of 3g.) was heated in a sealed tube with alcohol (23.4c.c.) and ammonia (d .880, 6.6c.c.) (equivalent to 30c.c. 4N NH_4OH) for 8 hr. at 180°. Out of four tubes only one showed signs of charring. The contents of the tubes were poured into cold water and the yellow solid which separated was crystallised from 50% alcohol. (In case of charring some animal char was used). The 2-nitro-5-chloro-aniline formed fine yellow needles m.p. 123-124°. (de Bruyn, loc. cit., gives m.p. 123.5°.).

Condensation of 2-nitro-5-chloro-aniline with K o-bromobenzoate

2-Nitro/

2-Nitro-5-chloro-aniline (3.4g.), K o-bromobenzoate (4.8g.), amyl alcohol (10c.c.), and Cu powder (0.1g.) were refluxed for 5 hr. in an oil-bath. The reaction product was made alkaline with caustic soda, the amyl alcohol distilled in steam, and the residue cooled and filtered from some unchanged 2-nitro-5-chloro-aniline and the filtrate made acid with dilute HCl. After a short time a reddish solid separated. Crystallised from glacial acetic acid two sets of crystals were obtained, a yellow needle-shaped form m.p. 226-228°, and a flat plate type (perhaps cubic ?) m.p. 228°. The yellow needle-shaped form on standing for several hours gradually changed into a slightly more reddish powder suggesting that this is an unstable form of 2-nitro-5-chloro-diphenylamine-6'-carboxylic acid (XLI). The yield from this experiment was small and the compound was obtained in larger quantity by the following preparation.

2-Nitro-5-chloro-diphenylamine-6'-carboxylic acid (XLI).

K anthranilate (4.36g.), 2:4-dichloro-nitrobenzene (4.8g.), amyl alcohol (10c.c.), and Cu powder (0.1g.) were heated under reflux in an oil-bath for $3\frac{1}{2}$ hr. at such a temperature that the alcohol gently refluxed. It was noticed that solution soon took place and shortly after solid began to separate. When the reaction was judged complete, the reaction mixture was made alkaline with caustic soda solution, and the amyl alcohol driven off in steam. The residue was cooled, filtered, and the filtrate acidified with dilute HCl, when a brownish-yellow solid separated. After filtration this was crystallised from glacial acetic acid when two sets of crystals were obtained (see above). It was noticed that the darker cubic (?) form did not dissolve as readily as the yellow needle-shaped form and by careful/

careful fractional solution it was possible to separate the two forms. Further, a small quantity of the reddish cubic form crystallised quickly from glacial acetic acid gave the long needle-shaped forms with no sign of the cubic. This may be taken as proof of dimorphism.

From two experiments the yield of crude (mixed forms) was 5g. from which 2.7g. of the reddish cubic form m.p. 228° was obtained and a smaller quantity of the yellow long needle-shaped form. (Cubic form--Found: Cl, 12.7. Needle-shaped form--Found: Cl, 11.93. $C_{13}H_9O_4N_2Cl$ requires Cl, 12.14%). While working with this compound it was noticed that it had sternutatory properties.

1-Nitro-4-chloro-acridone (XIV).

2-Nitro-5-chloro-diphenylamine-6'-carboxylic acid (4.7g.) and H_2SO_4 (d 1.84, 33c.c.) were heated on a boiling water-bath for 20 min., cooled, and poured into cold water. The orange-yellow solid which separated was filtered and boiled with dilute sodium carbonate solution, then with water, and washed with hot water. The solid left was boiled up with a large quantity of slightly diluted acetic acid when the yellow solid gradually dissolved and there was deposited a brownish-red solid forming tabular crystals. This was separated from the mother-liquor, boiled up again with slightly diluted acetic acid and filtered hot. The residue on drying formed reddish tabular plates in appearance very like 2-nitro-5-chloro-diphenylamine-6'-carboxylic acid but with m.p. 238-240° (10° higher than the acid), and while the acid is soluble in dilute Na_2CO_3 solution the new acridone is insoluble in that reagent. The yield of 1-nitro-4-chloro-acridone was 3.7g. (84% Theory). Recrystallised from nitrobenzene it had

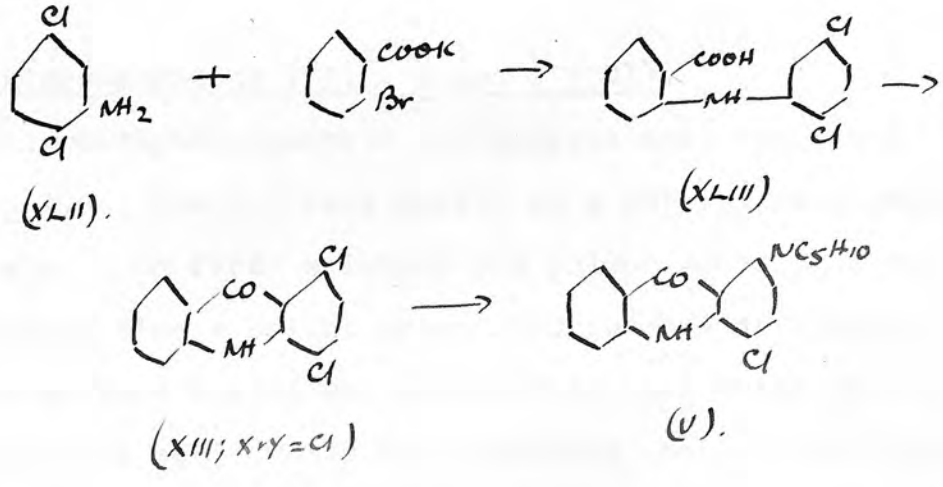
m.p./

m.p. 240°. (Found: Cl, 13.17. $C_{13}H_7O_3N_2Cl$ requires Cl, 13.0%).

2-Nitro-4-piperidyl-acridone (XV).

2-Nitro-4-chloro-acridone (1.36g.) and piperidine (7c.c.) were heated under reflux in an oil-bath when in a very short time the red of the nitro-chloro-acridone changed to yellow. To complete the reaction the mixture was boiled for 2 hr. when some white solid (piperidine hydrochloride) was noticed in the tube. After cooling and pouring into cold water a bright orange-yellow solid separated. This was filtered, washed at the pump with cold water, and crystallised from dilut alcohol in small fine orange-yellow needles m.p. 192°. Yield 1.6g. (almost theoretical). Compound contained no halogen. (Found: N, 13.28. $C_{18}H_{17}O_3N_3$ requires N, 13.0%).

Synthesis 4.



(XLII). (XLIII) (XIII; X+Y=Cl) (V).

2:5-Dichloro-aniline (XLII) was condensed with K o-bromo-benzoate to give 2:5-dichloro-diphenylamine-6'-carboxylic acid (XLIII) which with sulphuric acid gave 1:4-dichloro-acridone (XIII, X and Y = Cl). On heating with piperidine this/

this lost only one Cl atom, that in the 4 position, to give the 1-chloro-4-piperidyl-acridone (V) which was identical with the compound already obtained by the action of piperidine on 1-chloro-4-nitro-acridone (Synthesis 1, page 49).

2:5-Dichloro-diphenylamine-6'-carboxylic acid (XLIII).
2:5-Dichloro-aniline (3.25g.), K o-bromobenzoate (4.8g.), amyl alcohol (10c.c.), and Cu powder (0.1g.) were refluxed in an oil-bath for 5 hr. On diluting with cold water the K salt of the condensation product separated but on making alkaline with dilute caustic soda it dissolved again. The amyl alcohol was distilled off in steam, the residue filtered hot, and the filtrate made acid with dilute HCl when a cream-coloured solid separated. After filtration and crystallisation from glacial acetic acid 2:5-dichloro-diphenylamine-6'-carboxylic acid formed greyish-white needles m.p. 232°. Yield 2.7g. (48% Theory). (Found: Cl, 24.4. $C_{13}H_9O_2NCl_2$ requires Cl, 25.1%).

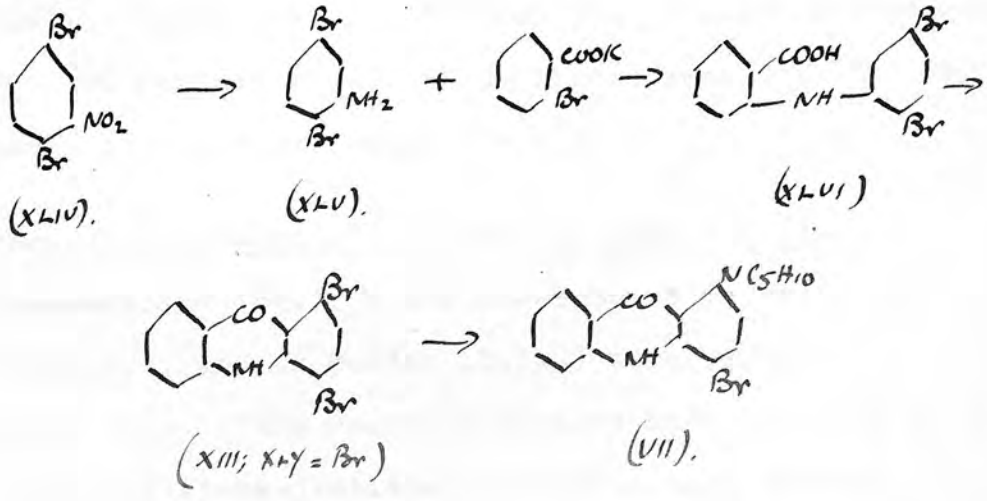
1:4-Dichloro-acridone (XIII, X and Y = Cl).
2:5-Dichloro-diphenylamine-6'-carboxylic acid (5g.) and H_2SO_4 (d 1.84, 35c.c.) were heated on a boiling water-bath for 20 min. On first solution the colour was slight but in a very short time a bright green fluorescence developed. The reaction mixture cooled and poured into cold water gave a lemon-coloured solid which was separated, boiled with water, then with dilute sodium carbonate solution, and again with water, dried in a steam-oven and crystallised from nitro-benzene. 1:4-Dichloro-acridone forms micro-crystalline yellowish needles m.p. 268°. Yield 3g. (64% Theory). (Found: Cl, 26.42. $C_{13}H_7ONCl_2$ requires Cl, 26.9%).

Action/

Action of piperidine on 1:4-dichloro-acridone.

1:4-Dichloro-acridone (1.32g.) and piperidine (7c.c.) were heated in an oil-bath so that the piperidine just refluxed. After about 1 hr. white crystals of piperidine hydrochloride were noticed on the side of the tube and after 2 hr. all the acridone had gone into solution and only the piperidine hydrochloride crystals were observed. By filtering hot these were separated and the filtrate poured into cold water separated a bright yellow solid which crystallised from dilute alcohol gave 1-chloro-4-piperidyl-acridone (V). (M.p. 110°; mixed m.p. with that already prepared Synthesis 1 page 49 showed no depression). Yield 1.2g. (77% Theory).

Synthesis 5.



2:5-Dibromo-nitrobenzene (XLIV) was reduced by West's method (J.C.S., 1925, 494) to give 2:5-dibromo-aniline (XLV) which condensed with K o-bromobenzoate gave 2:5-dibromo-diphenylamine-6'-carboxylic acid (XLVI). This with sulphuric acid gave 1:4-dibromo-acridone (XIII, X and Y = Br) which on heating with piperidine lost one bromine atom (4) to give 1-bromo-4-piperidyl-acridone (VII) identical with that already prepared by the action of piperidine on 1-bromo-/

1-bromo-4-nitro-acridone (Synthesis 2, page 51).

Reduction of 2:5-dibromo-nitrobenzene.

2:5-Dibromo-nitrobenzene (50g.) was dissolved in spirit (150c.c.) and HCl (d 1.12, 5c.c.). The mixture was heated to boiling on the water-bath and iron filings (35g.) added in four portions allowing five minutes between each addition. The reaction mixture was kept at vigorous ebullition and the heating continued for 2 hr. after the final addition of the iron. After making alkaline with caustic soda solution, the mixture was steam-distilled and the aqueous portion of the distillate containing the solid dibromoaniline collected separately. The solid, after filtration and crystallisation from alcohol slightly diluted with water, formed white prisms m.p. 53-54°. Yield 35g. (78% Theory). (Meyer and Stuber, Ann., 165, 180 reduced 2:5-dibromo-nitrobenzene with tin and hydrochloric acid and give m.p. 51-52°).

2:5-Dibromo-diphenylamine-6'-carboxylic acid (XLVI).

2:5-Dibromo-aniline (5g.), K o-bromobenzoate (4.8g.), amyl alcohol (10c.c.), and Cu powder (0.1g.) were refluxed in an oil-bath for 6 hr. The reaction mixture made alkaline with caustic soda was steam-distilled to remove amyl alcohol, the residue filtered and the filtrate made acid with dilute hydrochloric acid. The dirty-white solid which separated was washed at the pump and crystallised from glacial acetic acid in greyish-white needles m.p. 229-230°. Yield from two experiments 5.3g. (36% Theory). (Found: Br, 42.8. $C_{13}H_9O_2NBr_2$ requires Br, 43.13%).

1:4-Dibromo-acridone (XIII, X and Y = Br).

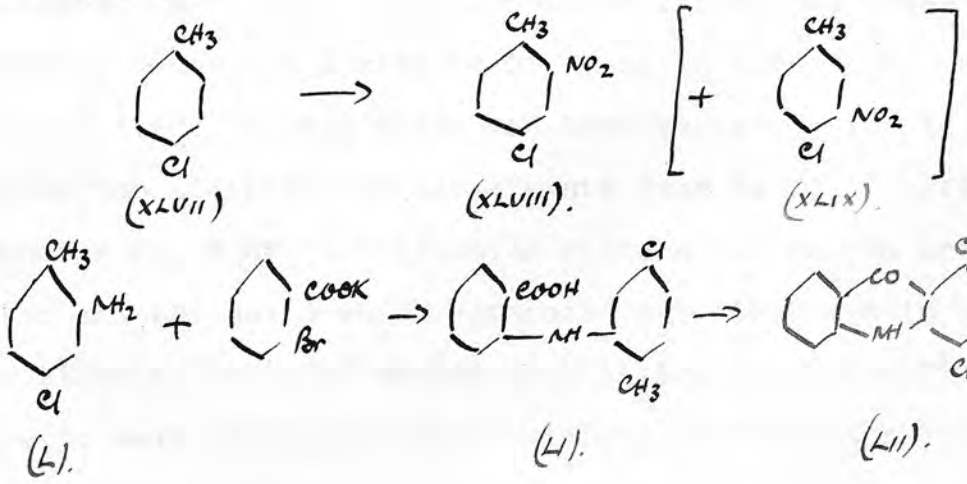
2:5-Dibromo-diphenylamine-6'-carboxylic acid (4g.) and H_2SO_4 (d/

(d 1.84; 28c.c.) were heated on a boiling water-bath for 20 min. The solution soon developed a green fluorescence. When cooled and poured into water a pale yellow solid separated. This was filtered, boiled with water, then with dilute sodium carbonate solution and again with water, dried in a steam-oven and crystallised from nitrobenzene. 1:4-Dibromo-acridone formed pale yellow needles m.p. 232-233°. Mixed m.p. with original diphenylamine-carboxylic acid 198°. Yield 2.1g. (55% Theory). (Found: Br, 44.8. $C_{13}H_7ONBr_2$ requires Br, 45.3%).

Action of piperidine on 1:4-dibromo-acridone.

1:4-Dibromo-acridone (1g.) and piperidine (6c.c.) were heated under reflux in an oil-bath so that the piperidine just refluxed. In about 10 min. a clear solution was obtained and the heating was continued for ½ hr. to complete the reaction. The reaction mixture poured into cold water gave a bright yellow solid which crystallised from dilute alcohol in yellow needles m.p. 112° decomp. after softening at 102°. Yield 0.9g. (89% Theory). This gave no depression in mixed m.p. with 1-bromo-piperidyl-acridone prepared by the action of piperidine on 1-bromo-4-nitro-acridone.

Synthesis 6.



p-/

p-Chlorotoluene (XLVII) was nitrated to give a mixture of 2-nitro-4-chlorotoluene (XLVIII) and 3-nitro-4-chlorotoluene (XLIX). The former was reduced by West's method (J.C.S., 1925, 494) to give 2-methyl-5-chloro-aniline (L) and this condensed with K o-bromobenzoate gave 2-methyl-5-chloro-diphenylamine-6'-carboxylic acid (LI) which with sulphuric acid gave 1-methyl-4-chloro-acridone (LII). This acridone is unchanged on heating with piperidine.

Nitration of p-chlorotoluene.

This has been studied by Goldschmidt and Hönig (Ber., 1886, 19, 2440) and in more detail by Hollemann and van der Arend (Rec. trav. chim., 1909, 28, 418) and by Shaw and Turner (J.C.S., 1932, 1884). The last two workers give the following results for nitration under conditions which were used in the preparation given below, the approximate yields from which are also given in the Table.

	Temp.	Isomerides %.	
		2-Nitro-	3-Nitro-
S. and T.	0°-50°	58.8	41.2
N.	0°-50°	37.5	25.8.

p-Chlorotoluene (100g.) was cooled in ice till crystals began to appear (m.p. 7.4°) and the cooled liquid was added from a dropping funnel to a mixture of H_2SO_4 (d 1.84; 100c.c.) and HNO_3 (d 1.48; 86c.c.) which had been cooled in ice to 0°. During the addition the temperature rose to 50°. After standing for 2 hr. the reaction mixture was poured into ice water and the solid which separated was dissolved in ether, the etherial solution washed with water, then with dilute caustic soda, and again with water, dried over anhydrous calcium/

calcium chloride and distilled. The fraction b.p. 250-260° at 766.5mm. was collected. Yield 98g. (72.2% Theory for mixed nitro compounds). The mixture was then redistilled and the following fractions collected separately:-

Fraction 1.	B.p. 250-254°.	48g.	Went solid on cooling in water.
Fraction 2.	B.p. 254-256°.	22g.	do. do.
Fraction 3.	B.p. 256-262°.	21g.	Gave small quantity of solid on standing overnight.

The solid which separated out was filtered off (51g. m.p. 30°) from the liquid portion (35g.) and crystallised twice from light petroleum (b.p. 40-60°) had m.p. 37-38°. The 2-nitro-4-chlorotoluene so obtained formed stout pale yellow needles.

p-Chloro-o-toluidine (2-methyl-5-chloro-aniline) (L).

2-Nitro-4-chlorotoluene has been reduced to the corresponding aniline by Goldschmidt and Hönig (loc. cit.) by reduction with tin and hydrochloric acid when p-chloro-o-toluidine was obtained mixed with some compound which was probably dichlorotoluene (?). Using West's method of reduction (loc. cit.) the reduction of 2-nitro-4-chlorotoluene proceeds easily and gives 74% yield of the desired chlorotoluidine. 2-Nitro-4-chlorotoluene (28g.) was dissolved in spirit (100c.c.) and HCl (d 1.12; 3c.c.) and heated to boiling on the water-bath. Iron filings (28g.) were added in four portions allowing five minutes between each addition. The mixture was then boiled under reflux for 2 hr., made alkaline and steam-distilled. The milky distillate which passed over after the alcohol had distilled was collected separately, extracted with ether, the etherial solution dried over anhydrous potassium carbonate and distilled.

The/

The base was collected in the fraction b.p. 246-247° at 759mm. Yield 17g. (74% Theory). (Goldschmidt and Hönig give b.p. 237° at 722mm.). 2-Methyl-5-chloro-aniline was completely identified by formation of its acetyl derivative - white needles from very dilute alcohol m.p. 130-131°. (c.f. Goldschmidt and Hönig, loc. cit., 2441).

2-Methyl-5-chloro-diphenylamine-6'-carboxylic acid (LI). 2-Methyl-5-chloro-aniline (2.8g.), K o-bromobenzoate (4.8g.), amyl alcohol (10c.c.) and Cu powder (0.1g.) were heated under reflux in an oil-bath for 3 hr. The reaction mixture was made alkaline with caustic soda solution, the amyl alcohol distilled in steam, and the hot residue filtered from a greenish solid. The filtrate on acidifying with dilute hydrochloric acid gave a pale yellow solid which crystallised in lemon coloured needles from acetic acid slightly diluted with water, m.p. 180-181°. Yield 3.1g. (60% Theory). (Found: Cl, 13.0. $C_{14}H_{12}O_2NCl$ requires Cl, 13.1%).

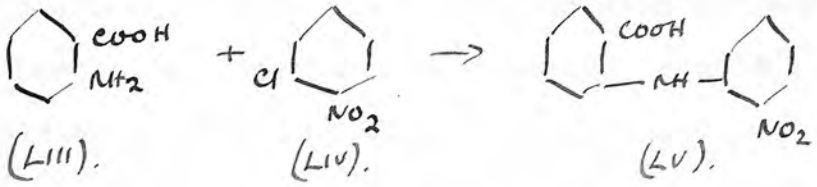
1-Methyl-4-chloro-acridone (LII).
2-Methyl-5-chloro-diphenylamine-6'-carboxylic acid (5.3g.) and H_2SO_4 (d 1.84; 37c.c.) were heated on a boiling water-bath for 20 min. A strong greenish fluorescence developed during the heating. The reaction mixture, after cooling, was poured into cold water, and the solid which separated was washed with hot water and crystallised from glacial acetic acid. 1-Methyl-4-chloro-acridone formed small pale yellow needles m.p. 298°. Yield 3.7g. (75% Theory). (Found: Cl, 14.5. $C_{14}H_{10}ONCl$ requires Cl, 14.55%).

Action of piperidine on 1-methyl-4-chloro-acridone.

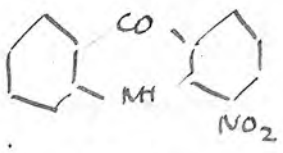
1-/

1-Methyl-4-chloro-acridone (1.5g.), piperidine (10c.c.) and a trace of copper powder were boiled under reflux for 9 hr. The liquid darkened a little but there was no sign of solution. The mixture was filtered hot and the residue washed with alcohol and dried m.p. 298° (mixed m.p. with original acridone showed no depression). Recovered 1.3g.

Synthesis 7.



(LIII). (LIV). (LV).



(XIX)

o-Chloro-nitrobenzene (LIV) was condensed with anthranilic acid (LIII) to give 2-nitro-diphenylamine-6'-carboxylic acid (LV) and this with sulphuric acid gave 1-nitro-acridone (XIX). (The methods of Clemo, Perkin and Robinson, (J.C.S., 1924, 1770) were used in these preparations). 1-Nitro-acridone did not react with piperidine in the presence of sodamide (c.f. Bradley and Robinson (J.C.S., 1932, 1255)).

Preparation of 2-nitro-diphenylamine-6'-carboxylic acid. Anthranilic acid (68.5g.), o-chloro-nitrobenzene (100g.), anhydrous K_2CO_3 (69g.) and Cu powder (0.1g.) were heated in a flask fitted with a stirrer and a wide tube attached to a condenser to collect any water given off. The temperature was kept at 200° when the mixture melted and solidified again.

After/

After about 1 hr. the mass which had gone almost solid was heated up at 220° and after about a further hour changed to a liquid. This on heating and stirring (1 hr.) changed to a stiff paste and finally to a solid. The temperature was kept at 220° for a further hour and then the reaction product was allowed to cool. The solid was dissolved in 500-600c.c. hot water and steam-distilled to remove any unchanged o-chloro-nitrobenzene. (This took 4-6 hr.). The solution, after cooling, was acidified with HCl and the olive-green precipitate broken up, collected, washed and dried. Yield of crude acid 130g.; crystallised from glacial acetic acid in very dark olive-green needles m.p. 219°.

1-Nitro-acridone (XIX).

130g. crude 2-nitro-diphenylamine-6'-carboxylic acid was heated on a boiling water-bath for 20 min. with H_2SO_4 (d 1.84; 700c.c.). After cooling, the resulting solution was poured on to ice and left overnight. The precipitate was collected, boiled with water, then with dilute sodium carbonate solution, and again with water and dried in a steam-oven. Yield of crude acridone 80g. Crystallised from nitrobenzene it formed dark yellow-green needles m.p. 257°.

Action of piperidine on 1-nitro-acridone.

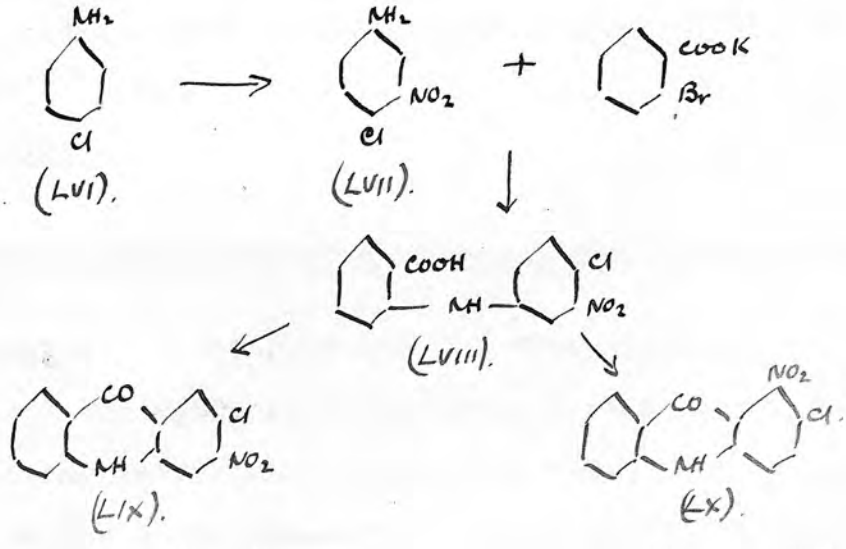
The 1-nitro-acridone used in this experiment was crystallised twice from nitrobenzene and washed with alcohol to improve the colour -- no change in m.p.

1-Nitro-acridone (2.4g.), sodamide (0.4g.) and piperidine 10c.c. were heated under reflux for 1 hr., stood overnight, and again boiled for 2 hr. with no evidence of any reaction. On cooling and adding water, ammonia was given off from the/

the sodamide. The mixture was then made acid with dilute HCl and filtered. The filtrate on basifying with ammonia gave no precipitate. The residue (2.3g.) crystallised from nitrobenzene in micro-crystalline needles m.p. 257° and was identical with 1-nitro-acridone.

Note. In Bradley and Robinson's work on the replacement of hydrogen para to a nitro group in a benzene ring it was suggested that the reaction proceeds at the expense of part of the nitro compound i.e. the liberated H atom reduces part of the nitro compound. In this case the insolubility of the nitro-acridone in piperidine may cause failure to give the necessary supply of oxidising agent and so prevent the reaction.

Synthesis 8.



p-Chloro-aniline (LVI) was nitrated to m-nitro-p-chloro-aniline and this condensed with K o-bromobenzoate gave 3-nitro-4-chloro-diphenylamine-6'-carboxylic acid (LVIII). This on acridonation should give a mixture of 2-nitro-3-chloro-acridone (LIX) and 3-chloro-4-nitro-acridone (LX). On carrying out the experiment two compounds were obtained but in view of the difficulty in proving their constitution this/

this has not been fully investigated.

Nitration of p-chloro-aniline (see Part II, page 42).

3-Nitro-4-chloro-diphenylamine-6'-carboxylic acid (LVIII). 3-Nitro-4-chloro-aniline (3.4g.), K o-bromobenzoate (4.8g.), amyl alcohol (10c.c.) and Cu powder (0.1g.) were refluxed in an oil-bath for 4-6 hr. The reaction product was made alkaline with caustic soda and steam-distilled to remove amyl alcohol. The residue was cooled, filtered from a small amount of precipitate (3-nitro-4-chloro-aniline ?) and the filtrate made acid with dilute HCl when a yellow solid separated. This was filtered, washed with water and dried in a steam-oven. Yield of crude acid 3.5g. Crystallised from acetic acid slightly diluted with water 3-nitro-4-chloro-diphenylamine-6'-carboxylic acid formed long dark brownish-yellow needles which crushed to an orange-yellow powder m.p. 188°. (Found: Cl, 12.35. $C_{13}H_9O_4N_2Cl$ requires Cl, 12.14%).

Acridonation with 3-nitro-4-chloro-diphenylamine-6'-carboxylic acid.

Experiment 1. 3-Nitro-4-chloro-diphenylamine-6'-carboxylic acid (4g.) and H_2SO_4 (d 1.84; 28c.c.) were heated for 15 min. on a boiling water-bath, cooled and poured into cold water when a yellow solid separated. This was filtered, washed with water, boiled with dilute sodium carbonate solution, then with water, filtered and dried in a steam-oven. Yield of crude product 1.5g. Crystallised from glacial acetic acid slightly diluted with water this gave an orange-yellow solid m.p. 326° (quite sharp in spite of evidence of a crystalline body mixed with a yellowish powder). The alkaline mother-liquor from boiling with sodium carbonate deposited/

deposited an orange-red sodium salt (presumably of unchanged diphenylamine-carboxylic acid). This was collected, washed with a very small quantity of cold water, dissolved in hot water and precipitated with dilute HCl. The bright yellow solid which separated was filtered, washed with dilute HCl and crystallised from diluted acetic acid when brownish-yellow needles were obtained m.p. 188° (identical with the original 3-nitro-4-chloro-diphenylamine-6'-carboxylic acid). From this experiment it was judged that the time allowed for acridonation had been too short and consequently the conditions given below were investigated.

Experiment 2. 3-Nitro-4-chloro-diphenylamine-6'-carboxylic acid (1g.) in H_2SO_4 (d 1.84; 10c.c.) was placed on a cold water-bath which was then brought to the boil and kept boiling for 20 min. After cooling, the solution was poured into cold water and the solid which separated filtered, washed with water, boiled with dilute sodium carbonate solution, then with water, and finally collected and dried in a steam-oven. Yield of crude product 0.7g. This crystallised from glacial acetic acid gave a small crop of brownish-yellow needles m.p. 360°, and the mother-liquor, on diluting, gave a small quantity of powdery solid m.p. 328-330°. It is suggested that these two solids are the acridones (LIX) and (LX).

Further examples of acridone synthesis have been given in Part I of this thesis.

Action/

Action of Piperidine on Halogenated Anilines.

1. Action of piperidine on 5-nitro-2-chloro-aniline (VIII; X = Cl).

Preliminary experiments (heating under reflux at such a temperature that piperidine just boiled) showed that piperidine at its b.p. had little effect on 5-nitro-2-chloro-aniline since most of the nitro-chloro-aniline was recovered unchanged. Heated in a sealed tube, however, chlorine was replaced by piperidyl.

5-Nitro-2-chloro-aniline (6.68g.) and piperidine (7c.c.) were heated in a sealed tube at 180-200° for 6 hr. and then cooled. Crystals of piperidine hydrochloride were observed in the tube the contents of which were warmed out with water and then with alcohol, poured into 400c.c. cold water when a dark reddish-brown oil separated and soon became solid. Crystallised twice from spirit this gave 2-piperidyl-5-nitro-aniline (IX) as chocolate-brown needles (3.3g.) m.p. 79-81°. (Found: N, 19.4. $C_{11}H_{15}O_2N_3$ requires N, 19.0%).

11. Action of piperidine on 5-nitro-2-bromo-aniline (VIII; X = Br).

5-Nitro-2-bromo-aniline (2.17g.) and piperidine (4c.c.) were heated in a sealed tube at 180-200° for 6 hr. The product of the reaction was isolated as in (1) and was found to be 2-piperidyl-5-nitro-aniline (IX) m.p. 79-81°. (Mixed m.p. with the sample obtained above showed no depression). Yield 1g.

111. Action of piperidine on 2-nitro-5-chloro-aniline and on 3-nitro-4-chloro-aniline.

This was examined both at the b.p. of piperidine and in a sealed/

sealed tube at 180-200°; but in neither case was it possible to isolate products in which chlorine had been replaced by piperidyl. At the lower temperature the nitro-halogenated aniline was recovered and at the higher temperature charring and decomposition took place in both cases.

PART IV.

AN ATTEMPT to CORRELATE SUBSTITUTION and REPLACEMENT in the BENZENE NUCLEUS.

Although it has been known for a very long time that groups generally regarded as positive could be replaced by negative groups e.g. o-dinitrobenzene on treatment with alkali gives o-nitrophenol, no evidence was available that nuclear hydrogen could be replaced directly by a negative group. Bradley and Robinson (1), however, have now shown that hydrogen may be replaced (substituted) by a group such as piperidyl. In view of this, therefore, it seems desirable at least to attempt to correlate the principles underlying substitution for hydrogen and replacement of other groups.

Groups which may be present attached to a benzene ring may be divided into three classes:-

(a) Cationoid (positive) groups i.e. those which attract electrons, generally recognised as meta orienting for substitution of a second cationoid group (e.g. $-NO_2$, -CO-R, etc.)

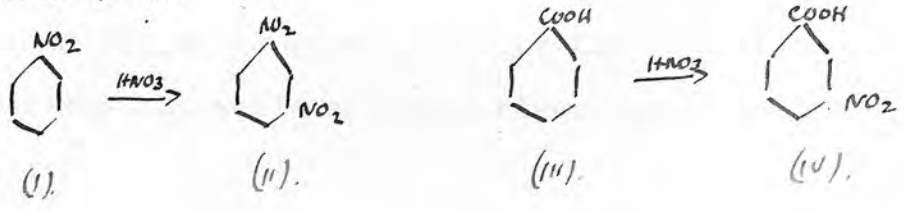
(b) Anionoid (negative) groups i.e. those which repel electrons, generally recognised as ortho and para orienting for substitution of a cationoid group (e.g. Cl, Br, $-CH_3$, etc.).

(c) Hydrogen must be put in a special class since it seems to have little influence on other groups substituted in the nucleus.

Reagents/

Reagents which may attack the nucleus may be classified under two heads (a) cationoid, (b) anionoid (2). In the former, whatever explanation we may give to the mechanism of the reaction, a cationoid (positive) group becomes attached to the nucleus (NO_2 in nitration), while in the latter an anionoid (negative) group enters (OMe, NC_5H_{10}, NH_2, etc.).

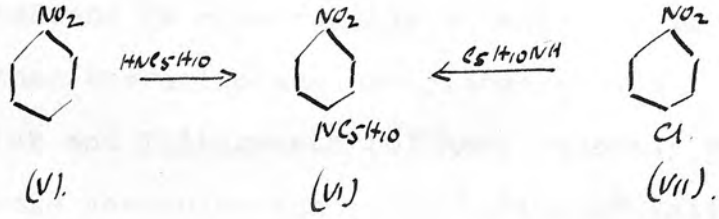
A cationoid group already substituted in the nucleus has a profound effect on the reactivity of other groups and of hydrogen attached to the nucleus. When attacked by a cationoid reagent substitution for hydrogen takes place at the position meta to the already substituted group, while attack by an anionoid reagent may result in the replacement of hydrogen or other groups in the ortho or para positions.
Examples of cationoid attack:-
Nitrobenzene (I) on nitration gives mainly m-dinitrobenzene (II); benzoic acid (III) on nitration gives mainly m-nitro-benzoic acid (IV).

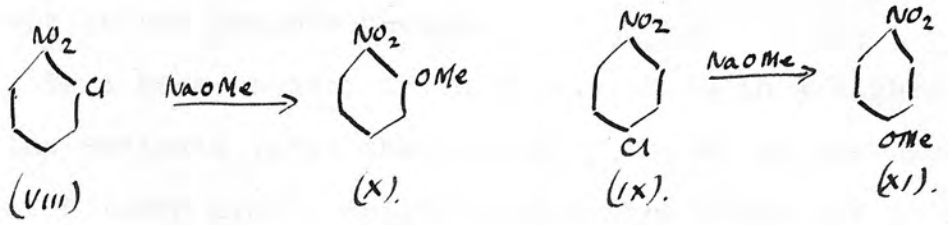


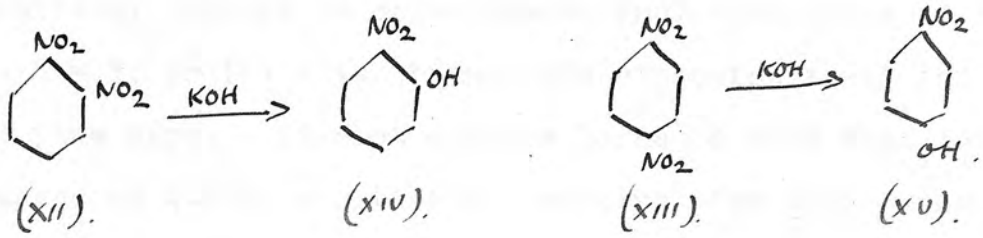
(I). (II). (III). (IV).

Examples of anionoid attack:-
Nitrobenzene (V) on treatment with piperidine gives 4-piperidyl-nitro-benzene (VI); the same compound is obtained on treating p-chloro-nitro-benzene (VII) with piperidine; o-chloronitrobenzene (VIII) and p-chloro-nitrobenzene (IX) on treatment with sodium methylate give the corresponding 2-nitro-anisole (X) and 4-nitro-anisole (XI); while even o-dinitrobenzene (XII) and p-dinitrobenzene (XIII)/

(XIII) on treatment with potassium hydroxide lose a nitro group to give o-nitrophenol (XIV) and p-nitrophenol (XV) respectively.



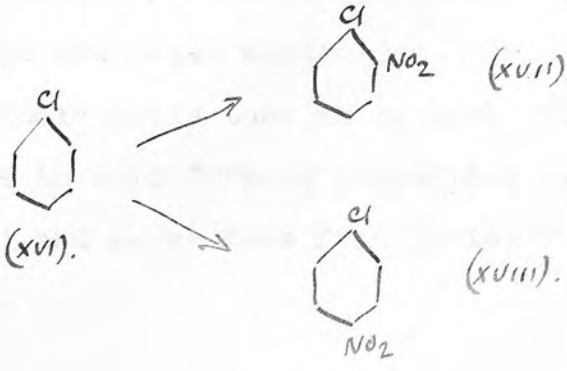




An anionoid group substituted in a nucleus activates the carbon in ortho and para positions for attack by cationoid reagents, while anionoid reagents attack the meta position.

Examples of cationoid attack:-

Chlorobenzene (XVI) on nitration gives a mixture of o-nitrochlorobenzene (XVII) and the para isomer (XVIII); aniline on nitration gives mainly para with smaller proportion of ortho derivatives.



Examples of anionoid attack:-
m-chloroaniline is slightly attacked by sodium methylate while p-chloro-aniline is not attacked at all (3); m-dichlorobenzene is more readily attacked by sodium methylate than the ortho and para isomers (4).

Hammick and Illingworth (5) have recently given the following rule governing the substitution of cationoid groups in the benzene nucleus:-
"If, in a benzene derivative Ph.X.Y, Y is in a higher group of the Periodic Table than X, or if, being in the same group, Y is of lower atomic weight than X, the group X.Y is meta-directive; whilst in other cases (including those in which (a) X = Y, or (b) Y is absent) the direction is of the ortho and para type. It must also be borne in mind that ionic charges on X.Y of positive or negative sign will cause meta or ortho and para orientation respectively".

They also state that the rule is without exception and in their paper explain the apparent anomaly of the nitroso group, which in nitrosobenzene directs an entering bromine atom to the para position at -5° in carbon disulphide, when according to the rule it should be substituted in the meta position. They show, however, that nitrosobenzene is considerably associated in carbon disulphide, and that in a dissociating solvent (acetic acid) bromination is slow and no para substitution takes place.

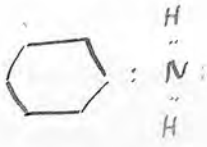
Such excellent agreement with the facts warrants a further study of the essential conditions. Now, it is a feature of the Periodic Table that as we pass from Group 0 - 7 we have an increase in acid forming properties (electro-negative character) and as we pass from Series 1 - 12 we have an/

an increase in base forming properties. It will be clear, then, that Hammick and Illingworth's rule for a group X.Y may be restated thus:- "Wherever Y is more acid (more electro-negative) than X we get meta substitution, whilst when Y is more basic (more electro-positive) than X we get ortho and para substitution".

Analysing this for X we can say that when X tends to be electro-positive we get meta substitution, and when the tendency is to electro-negative character substitution takes place in the ortho and para positions. (Note-- lone atoms (other than hydrogen) attached to the benzene ring tend to become electro-negative in character).

This gives a means of telling when the atom attached to a benzene ring is anionoid or cationoid in character.

With a somewhat similar idea in mind, Latimer and Porter (6) have made an attempt to calculate the residual charge on the substituted atom in each group, e.g. in the case of aniline



the positive charge on the N kernel is 5 and this is reduced by two unshared electrons, four electrons shared with hydrogen and two with carbon so that the residual charge is

$$5 - 2 - (4 \times \tfrac{1}{2}) - (2 \times 5/9) = -0.11.$$

When a pair of electrons is shared between two atoms it is assumed, except in the case of hydrogen, that the electrons are quantised in respect to the field between the atoms in the ratio of the positive charges on their kernels, e.g. in C : N, C has 2 x 4/9 and N 2 x 5/9 of the electronic charges. The bond between hydrogen and another atom cannot be so treated/

treated as it is known that the hydrogen ion is within the electron shell, or, at least, very close to the position of maximum electron density. Hence, in this case, it is considered that two electrons and one proton are so close together that their resultant charge is - 1. The relation between the residual charge and the percentage of ortho, meta and para nitro compounds obtained on nitration of various benzene derivatives is brought out in TABLE 1.

In general, when the residual charge is positive, cationoid substitution takes place in the meta position, and when negative, cationoid substitution takes place in the ortho and para positions.

The electronic conception of the structure of benzene and the course of organic reactions (7) suggests that the influence of a substituted group may make itself felt by either an inductive (general) effect (distortion of electron orbits) or by an electromeric effect (change in the distribution of shared and unshared electrons).

In the case of cationoid substituents the general effect will be to withdraw electrons from the nucleus and make it susceptible to attack by anionoid reagents and less easily attacked by cationoid reagents: and the reverse will be true of anionoid substituents in the nucleus. Further, if the electromeric effect of a cationoid substituent is such as to withdraw electrons from the nucleus (particularly from ortho and para positions) then this effect will be additive to the general effect and make such a compound very easily attacked by anionoid reagents (capable of giving electrons to the nucleus) at the ortho and para carbon atoms. Conversely, in the case of an anionoid substituent, if the electromeric/

electromeric effect is such as to push electrons into the nucleus (these accumulating on the ortho and para carbon atoms) this effect will be additive with the general effect and make the compound very easily attacked by cationoid reagents (those capable of taking up electrons) in the ortho and para positions.

Symbolising the above we may say that

1. Substituents with $+I+E$ effects give ease of anionoid attack at the ortho and para carbon atoms.

2. Substituents with $-I-E$ effects give ease of cationoid attack at the ortho and para carbon atoms.

In other cases in which the general or inductive effect opposes the electromeric effect it is easy to imagine that there will be cases in which

a. $+I$ will be greater than $-E$

b. $-E$ will be greater than $+I$

c. $-I$ will be greater than $+E$

d. $+E$ will be greater than $-I$

and, further, we may have substituents with only inductive or general effects $+I$ or $-I$.

It will be clear, then, that a group may be cationoid in both its general and electromeric effects, or anionoid in both, while in other cases the general and electromeric effects may oppose one another and the character of the substituent will vary according to the strength of the two effects.

The importance of the electromeric effect on cationoid attack has been investigated by Sutton (8) from data calculated from dipole moments. It is suggested that the electromeric moment, i.e. that moment which is produced by a change in/

in the distribution of shared and unshared electrons, is a very important factor in determining the orientating influence of a group. A close approximation to the value of this electromeric moment is calculated from the dipole moments of groups attached to alkyl and aryl radicals, M(alk) and M(arom), and it is pointed out that when the electromeric moment Me = M(arom) - M(alk) is positive (indicating a drift of electrons into the benzene nucleus) the group is invariably ortho and para orienting; and when it is negative (indicating a drift of electrons from the nucleus) the group directs to the meta position.

It is interesting to note the relation between the value of the electromeric moment and the percentage of ortho, meta and para isomers obtained on cationoid attack (nitration) given in TABLE 1.

TABLE 1./

TABLE 1.

	Electromeric Moment M(e) x 10^{-18} E.S.U.	* R.C.	Percentage of Isomers obtd. on Nitration. ortho.	meta.	para.
$-NH_2$	+0.32-+2.7	-0.11	1-2[7]	(49)[7]	98) (49)[7])
-OH	+0.95-+2.06	-0.2	59.2[6]	2.7[6]	38.1[6]
$-OCH_3$	+0.94-+1.04	-0.4			
-I	+0.88	-0.88	41.1[4]	0.0[4]	58.7[4]
-Br	+0.69	-0.8	37.6[4]	0.0[4]	62.4[4]
-Cl	+0.59	-0.62	30.1[4]	0.0[4]	69.9[4]
$-CH_3$	+0.45		58.8[3]	4.4	36.8[3]
$-CH_2Cl$	+0.21	+0.27	40.9[3]	4.2[3]) 15.5:12.0[6])	54.9
$-CHCl_2$	0.0	+0.55	23.3[3]	33.8[3]	42.9[3]
$-CCl_3$	-0.5	+0.82	6.8[3]	64.5[3]	28.7[3]
-COCH	-0.18	+1.20		66.9-90.0[5]	
-CO	-0.28				
$-CO_2H$		+1.4	18.5[4]	80.3[4]	1.2[4]
-C=N	-0.43	+1.2		80.53[8]	
$-NO_2$	-0.88	+1.26	6.4[2]) 6.8[4])	94.2[2]	0.4[2]
$-NMe_3$			0.0	100.0[10]	0.0

* R.C. = Residual Charge (Latimer and Porter, loc. cit.)

1. Flurscheim and Holmes, J.C.S., 1928, 1607.
2. Annual Reports Chem. Soc., 1925, 141.
3. Fry, Electronic Theory of Valency and the Structure of Benzene, p.125.
4. Do. Do. p.128.
5. Baker and Moffitt, J.C.S., 1931, 315, (increase in acid content increases meta product).
6. Arnall, J.C.S., 1924, 815.
7. Hollemann, Hartogs, and van der Linden, Ber., 1911, 44, 704-708: modified due to sulphate formation when nitrated in H_2SO_4. Believed nitrates mainly in para position with small quantity ortho c.f. Chem. Soc. Abst. 1911, 1, 364.
8. Baker, Cooper, and Ingold, J.C.S., 1928, 430.
9. Sutton, Proc. Roy. Soc. London, 1931, 133, 686.
10. Annual Reports Chem. Soc., 1928, 137.

It will be observed that with increase in negative value of the moment there is an increase in meta nitration, and with increase in the positive value of Me there is a corresponding increase in the proportion of ortho and para isomers isolated.

It is also of interest to observe the relation between

the/

the electromeric moment and the rate of replacement of such a group as Cl. Thus the accelerating influence on the rate of replacement of Cl by NaOMe varies through the series (9)

$NO_2 > CN > SO_3H > CO_2H > CH_2OH$

Me $-0.88 > -0.43$ - - - -

and the rate of attack by aqueous-alcoholic KOH on the chlorine atom in 2:4-disubstituted chloro-benzenes has been given by Davies and Wood (10)

NO_2	:	SO_3H	:	CO_2H
70,000	:	1	:	$\frac{1}{3}$

From the above considerations, it will be seen that the electromeric effect (as measured by Me) indicates what type of reaction will take place at the ortho and para positions:-

Me + Cationoid attack at o- and p- (-E).

Me - Anionoid attack at o- and p- (+E).

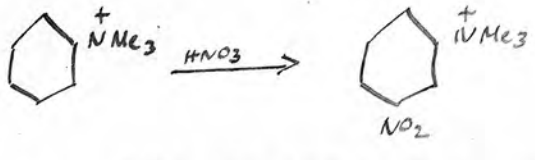
The general or inductive effect of a substituted group, however, cannot be neglected since such will help or hinder the electromeric effects and will, therefore, control in some measure the rate at which reaction takes place. This effect will be greatest where the substituted group carries an ionic charge e.g. in the phenoxide ion

the electromeric effect is backed up by the negative general effect and so makes ortho and para substitution by cationoid groups easy and complete (i.e. no meta).

There is some evidence available (11) that a positive ionic charge has the opposite effect in making the ortho and para positions easily substituted by anionoid reagents or halogen substituted there easily replaced by these reagents. Thus/

Thus, tribromo-aniline is converted (partially) into trichloro-aniline by concentrated hydrochloric acid at 200 , due no doubt to the halogen being activated by the free pole in the resulting aniline salt. The diazonium ion is a very powerful activator of halogen in the nucleus. Diazotised tribromo-aniline is easily converted into a trichlorobenzene diazonium salt, and p-chloro-aniline gives p-thiocyano-benzene diazonium thiocyanate.

While the evidence for the reactivity and ease of replacement at the ortho and para positions is still somewhat scanty, that for the effect of a positive pole on cationoid attack at the meta position is fairly well established. Nitration of the phenyl-trimethyl-ammonium ion gives 100% meta derivative:-



Further, the effect of a positive ionic charge may have more or less difficulty in making itself felt; the size of the atom may have an effect, e.g. in the series N, P, As, Sb, the positive character resident on the nucleus will have greater difficulty in making itself felt through the screen of electrons as the series is ascended. While no figures are available for the effect on anionoid attack at the ortho and para positions the percentages of meta derivative isolated in nitration are given in TABLE 11.

TABLE 11./

TABLE 11.

	Percentage meta nitro compound.
$PhN^{+}Me_3$	100
$PhP^{+}Me_3$	100
$PhAs^{+}Me_3$	98
$PhSb^{+}Me_3$	86

Again, the effect of a positive ionic charge has been shown to vary as it is attached directly to the nucleus or through a chain of carbon atoms (alkyl). This is brought out in TABLE 111 (13).

TABLE 111.

	Percentage meta nitro compound.
$PhCH_3$	4.4
$PhN^{+}Me_3$	100
$PhCH_2N^{+}Me_3$	88
$PhCH_2CH_2N^{+}Me_3$	19
$PhCH_2CH_3$	3 - 5
$PhNO_2$	93.2
$PhCH_2NO_2$	48
$PhCH_2CH_2NO_2$	13

The effect of the charge is damped by transmission through saturated carbon atoms. A similar effect is also noted in the case of nitro-compounds which are also included in TABLE 111.

This, of course, may be looked on in another way i.e. that the ortho and para orienting influence of the Me and Et groups is being reduced by the presence of cationoid groups replacing/

replacing hydrogen.

It will be clear from the foregoing that the influence of any group cannot be forecast in detail until we determine how it affects the reactivity of the ortho, meta and para positions for both cationoid and anionoid attack. Such figures might be regarded as a kind of "coefficient of reactivity" of each position when activated by a particular group. Even the nature of the attacking reagent (ionic or simply ionoid) will, no doubt, have an effect on the reactivity of each position and will have to be taken into consideration in attempting to forecast the orienting effect of a substituted group on an entering group.

An attempt to classify (in more detail than in the classification already given, page 78) substituted groups is given in TABLE IV page 85.

It will be seen that the groups fall into two genera which are identical with those already suggested (page 72) and in the main with the results of Hammick and Illingworth's, Latimer and Porter's, and Sutton's work.

To investigate the effect on substitutive and replacement reactions of each type of group is quite beyond the scope of the present correlation and would, indeed, be impossible with the data available. It is possible, however, to draw some general conclusions which are investigated in the sequel.

It is to be noted again that a substituted cationoid group makes the ortho and para carbon atoms cationoid, while a substituted anionoid group makes these carbon atoms anionoid and it is suggested that this is the primary effect of these groups and that the effect produced at the meta carbon/

carbon atom is only a secondary effect. The transmission of this primary effect will be affected in the main by electromeric changes which may or may not be facilitated by the inductive effect.

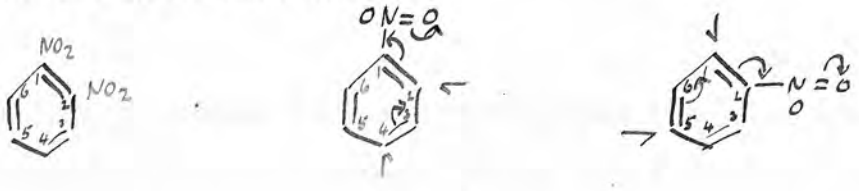
TABLE IV.

CLASSIFICATION of SUBSTITUTED GROUPS.

Genus.	Type.	Symbol.	Example.	Effect on Cationoid attack.	Effect on Anionoid attack.
Cationoid	1.	+I	$\overset{+}{N}Me_3$	Very difficult at meta	Very easy at ortho and para.
	2.	+I +E	NO_2. CN; CO; $COCH_3$	Difficult at meta.	Easy at ortho and para.
	3.	+E > -I	CCl_3.. $CHCl_2$..		
	4.	+E < -I	CH_2Cl..		
	5.	-E < +I	Cl	Difficult at ortho and para.	Difficult at ortho and para; slightly easier than Gp. 6 at meta.
Anionoid	6.	-E > +I	NH_2	Easy at ortho and para	Difficult at ortho and para; some evidence of attack at meta.
	7.	-I	CH_3	Easy at ortho and para	Difficult at ortho and para.
	8.	-E -I	$\bar{O}$	Very easy at ortho and para	Very difficult at ortho and para.

If, then, the cationoid or anionoid influence of a group is somehow transmitted through the double bond (Kekulé formula) to/

to the ortho carbon atom and through the conjugated double bond to the para carbon atom, this will necessitate a directional quality in this effect. Wherever this directional effect is such that the symmetry of the conjugated system in the Kekule formula is maintained, then normal results will follow; but where the characters of the substituted groups are such as to disturb the symmetry anomalous results will ensue. Substitution or replacement will take place in such a fashion as to restore as far as possible the symmetry in the nucleus. This will be clearly seen from the simple case of anionoid attack on o-dinitrobenzene

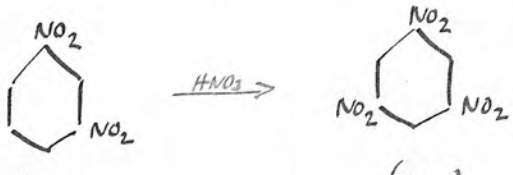


The nitro group in position 1 sends its influence along the double bond to C_2; while the nitro group at position 2 tends to send its influence along the same double bond from C_2 to C_1. With the replacement of the nitro group attached to C_2 by an anionoid group C_2 will receive the normal cationoid character which it would receive from the nitro group at C_1 and symmetry will be restored. This "tendency for a heterogeneous polarity to become homogeneous" (14) has long been recognised by electronic theories of the structure of benzene and its dependence on the symmetry of the Kekulé formula is one more evidence of the value of this early suggested structure of the benzene molecule.

When two groups (other than hydrogen) are substituted in a nucleus their influence on the reactivity of the other positions in the nucleus will be algebraically additive and may be either cumulative or oppose one another. The groups may/

may be two cationoid ($2NO_2$; $1NO_2$ and 1COR) or two anionoid groups (2Cl; $1NH_2$ and 1Cl) or one anionoid and one cationoid and in each case, of course, may be ortho, meta or para to one another.

In general, when groups are like, their influence on both cationoid and anionoid attack will be cumulative if they are meta to one another e.g. m-dinitrobenzene (XXII) nitrates wholly in the 5 position to give (XXIII).



(XXII). (XXIII).

and 2:4-dinitro-chlorobenzene (XXIV) has its chlorine more easily replaced by an anionoid group (NH_2) than the chlorine in o-nitro-chlorobenzene (XXV):

(XXIV). (XXV).

m-dichlorobenzene (XXVI) nitrates wholly in the 4 position to give 1:3-dichloro-4-nitrobenzene (XXVII) (15):

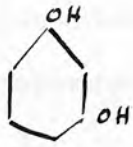
(XXVI). (XXVII).

1:3:5-trichlorobenzene (XXVIII) loses a chlorine atom more readily than 1:2:5-trichlorobenzene (XXIX) (16).

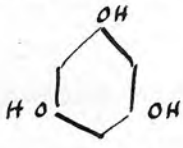
(XXVIII). (XXIX).

The/

The conversion of resorcinol (XXX) into phloroglucinol (XXX1) by fusion with potash may be cited as a case of cumulative effect of two anionoid groups in meta position to one another facilitating attack on the remaining meta position.

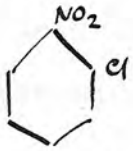


(XXX).

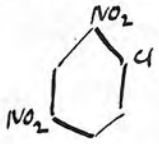


(XXX1).

In the case of nuclei substituted by one cationoid and one anionoid group the effect on both cationoid and anionoid attack will be cumulative if the two groups are either ortho or para to one another. Thus, o-nitro-chlorobenzene (XXX11) nitrates wholly in the 4 position to give (XXX111):



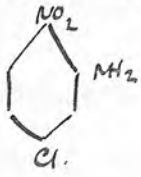
(XXX11).



(XXX111).

and 2:4-dichloro-nitrobenzene (XXX1V) on heating with ammonia is wholly converted into 2-nitro-5-chloro-aniline (XXXV) (17).

(XXX1V).

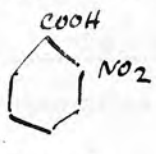


(XXXV).

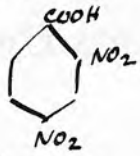
In all other cases the effect of two substituents will oppose one another and give rise to anomalous results. Examples of such cases will now be analysed seriatim.

Case 1. Two cationoid groups ortho to one another.

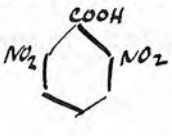
o-nitrobenzoic acid (XXXV1) on nitration gives a mixture of 2:4-dinitro-benzoic acid (XXXV11), 2:6-dinitrobenzoic acid (XXXV111) and 2:5-dinitro-benzoic acid (XXX1X):



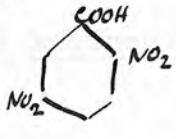
(XXXV1).



(XXXV11)



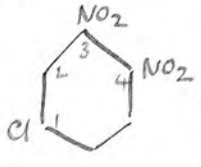
(XXXV111).



(XXX1X).

It will be seen at once, of course, that 1:2-dinitrobenzene gives the possibility of such anomalous results but that the anomaly disappears since 1:2:4-trinitrobenzene is identical with 1:2:5-trinitrobenzene and that 1:2:3- and 1:2:6-trinitro compounds are also identical.

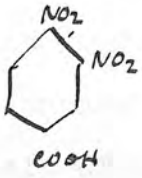
3:4-dinitrochlorobenzene (XL) on attack with an anionoid reagent has the 3-nitro group replaced to restore symmetry within the nucleus (18).



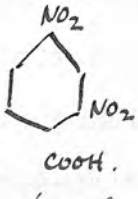
Case 11. Two Cationoid groups para to one another.

p-nitro-benzoic acid (XL1) on nitration gives a mixture of 3:4-dinitro-benzoic acid (XL11) and 2:4-dinitrobenzoic acid (XL111):

(XL1).

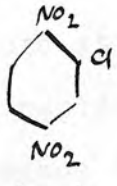


(XL11).

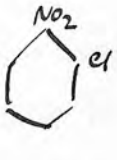


(XL111).

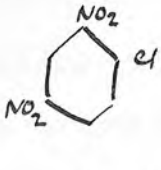
the anomaly in the case of 1:4-dinitrobenzene disappears because 1:3:4-trinitrobenzene is identical with 1:2:4-trinitro-benzene. 2:5-dinitro-chlorobenzene (XL1V) is attacked by sodium methylate more readily than 2-nitro-chlorobenzene (XLV) but not so readily as 2:4-dinitro-chlorobenzene (XLV1) (19).



(XL1V).



(XLV).

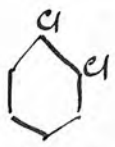


(XLV1).

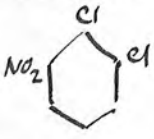
Case 111. Two Anionoid groups ortho to one another.

o-dichlorobenzene/

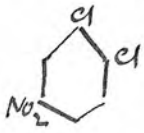
o-dichlorobenzene (XLV11) on nitration gives a mixture of 3- and 4-nitro-1:2-dichlorobenzene (XLV111) and (XL1X).



(XLVII).

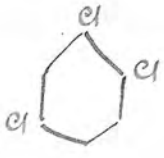


(XLVIII).



(XL1X).

1:2:4-trichlorobenzene (L) on attack by anionoid reagents has the Cl at position 2- removed. (20).

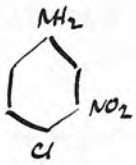


(L).

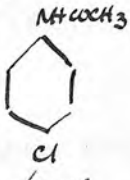
Case 1V. Two anionoid groups para to one another.

p-dichlorobenzene on nitration gives no anomaly since 1,3,5,6, positions are equal. p-chloroaniline (L1) nitrated in sulphuric acid solution loses its anomaly since the formation of the sulphate converts the N into a cationoid centre and the action of the substituted groups becomes cumulative on position 3 giving 100% yield of 3-nitro-4-chloro-aniline (L11) (21). In the nitration of p-chloroacetanilide (L111) the anionoid character of the N forces the entering group into the 2 position (L1V) (22).

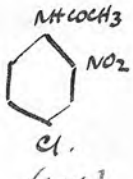
(L1).



(L11).



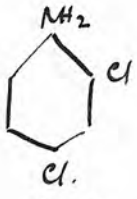
(L111).



(L1V).

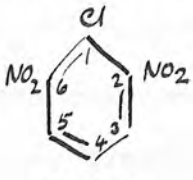
In an anionoid attack of a compound it is to be noted that a group to be replaced can only be meta to one of the anionoid groups and since it is ortho to the other anionoid attack will be inhibited by the ortho group e.g. 2:4-dichloroaniline (LV)/

(LV) loses no chlorine on prolonged heating with alcoholic potash (23).



(LV).

The directional symmetry effect may be one of the influences at work in making 2:6-dinitro-chlorobenzene (LVI) less susceptible to anionoid attack than 2:4-dinitro-chlorobenzene (LVII) (24).



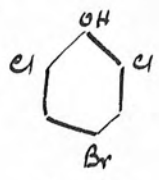
(LVI).

(LVII).

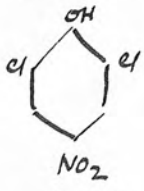
In the latter case the primary effects of the two nitro groups are cumulative on C_1; while in the former case although the two nitro groups are still meta to one another, with symmetry in the arrangement of the double bonds, only the 6-nitro group can influence C_1 along a single double bond, while the influence of the 2-nitro group has to be transmitted along a trienoid conjugated system. A similar effect may explain to some extent why 2:4-dinitro-toluene reacts readily with aldehydes to give stilbenes while 2:6-dinitro-toluene does not react as readily.

Replacement of groups other than hydrogen by cationoid groups may be brought into line with the ideas expressed above. A few examples from the literature may be cited (for a complete survey of this field c.f. de Lange, Rec. trav. chim., 1926, 45, 19 et seq.). 2:6-dichloro-4-bromo-phenol (LVIII) on nitration gives first 2:6-dichloro-4-nitro-phenol (LIX) and then/

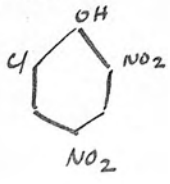
then 2:4-dinitro-6-chloro-phenol (LX) (25).



(LVIII).



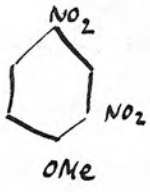
(LIX).



(LX).

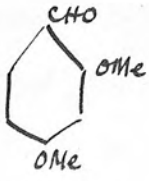
p-methoxybenzoic acid (LXI) on nitration gives 2:4-dinitro-anisole (LXII) (26).

(LXI).

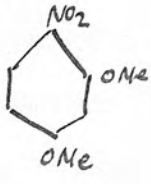


(LXII).

2:4-dimethoxybenzaldehyde (LXIII) on nitration gives 2:4-dimethoxy-nitro-benzene (LXIV) (27).

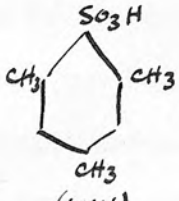


(LXIII).

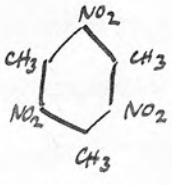


(LXIV).

Mesitylene sulphonic acid (LXV) on nitration gives trinitro-mesitylene (LXVI) (28).

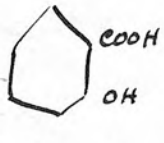


(LXV).

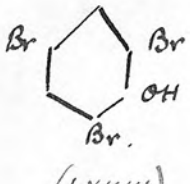


(LXVI).

Salicylic acid (LXVII) on bromination gives tribromophenol (LXVIII) (29).



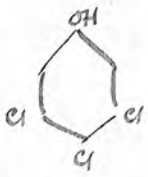
(LXVII).



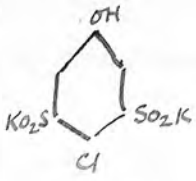
(LXVIII).

3:4:5-trichloro-phenol (LXIX) on treatment with potassium sulphite/

sulphite becomes (LXX) (30).



(LXIX).



(LXX).

de Lange (loc. cit.) noted the fact that if an anionoid group OH, NH_2, NHR, OR, or CH_3 is attached to a nucleus then groups in the ortho and para position (C ortho and C para very liable to cationoid attack) will be replaced if the group already present in ortho or para position precedes the replacing group in the series CO_2H, CHO, SO_3H, Br, Cl, NO_2. Here it is to be noted that all these groups are normally cationoid except Cl and Br; but in direct attack on a benzene compound by molecular chlorine or bromine we can postulate one atom anionoid and one cationoid and in this replacement it is the cationoid Cl or Br which replaces the group already in position.

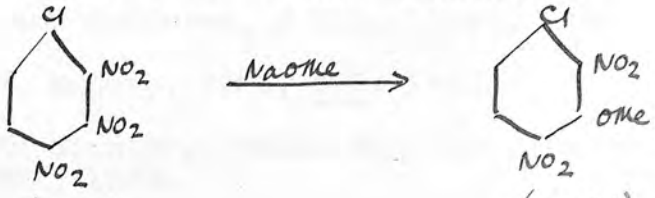
Without attempting to analyse in detail the effect of three substituted groups on the reactivity of a fourth substituent in a benzene ring the following cases on examination will prove to display the effects postulated above (31). 3:4:5-trinitro-chlorobenzene (LXXI) on treatment with sodium methylate is converted into 2:6-dinitro-4-chloro-anisole (LXXII).

(LXXI). (LXXII).

2:3:5-trinitro-chlorobenzene (LXXIII) gives 2:4-dinitro-6-chloro-anisole (LXXIV).

(LXXIII). (LXXIV).

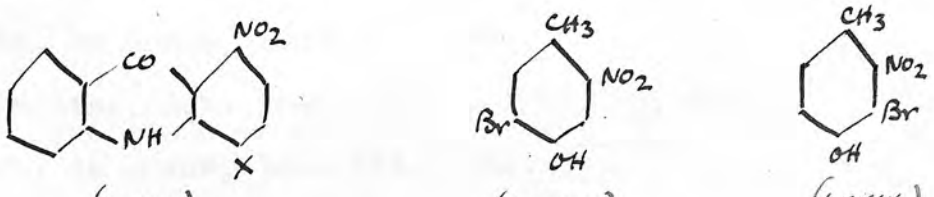
and 2:3:4-trinitro-chlorobenzene (LXXV) gives 2:6-dinitro-3-chloro-anisole (LXXVI) on similar treatment.



(LXXV). (LXXVI).

Further confirmation is added by the experiments described in Part III of this Thesis in which it has been shown that the heterogeneous polarity set up by two cationoid groups ortho to one another in 4-nitro-acridones (LXXVII) causes the nitro group to be replaced on anionoid attack.

A recent paper by Kermack and Spragg (32) may be discussed in the light of the foregoing attempted correlation. These workers have shown that the bromine atom in 2-nitro-5-bromo-p-cresol (LXXVIII) and in 2-nitro-3-bromo-p-cresol (LXXIX) is very inactive.



(LXXVII). (LXXVIII). (LXXIX).

Now, in the bromination of a phenol it is the cationoid Br atom which attaches itself in the ortho and para positions. Hence, here, the Br atom is cationoid and not anionoid as it must be for replacement by anionoid reagents. Even the influence of an ortho or para nitro group is insufficient to overcome the binding influence of the hydroxyl group which tends to preserve the cationoid character of the groups in the ortho position to itself.

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27. ibid., 49.

28./

28. ibid., 56-57.

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30. Armstrong and Harrow, Jahrsber., 1876, 447. c.f. Th de Crauw, loc. cit., 762.

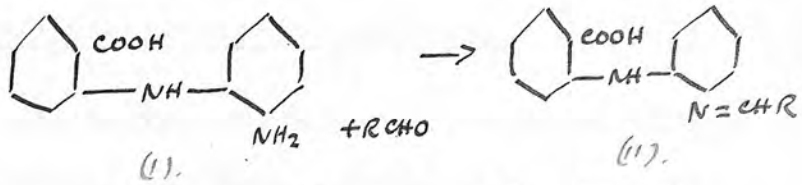
31. v. de Vliet, Rec. trav. chim., 1924, 43, 622.

32. Kermack and Spragg, J.C.S., 1932, 2946.

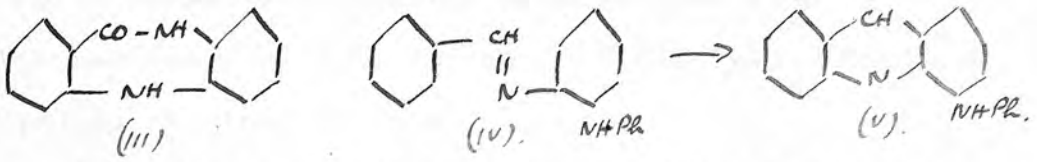
P A R T V.

BENZYLIDENE DERIVATIVES of 2-AMINO-DIPHENYLAMINE-6'-CARBOXYLIC ACID and 2-AMINO-DIPHENYLAMINE and their THERMAL DECOMPOSITION.

2-Amino-diphenylamine-6'-carboxylic acid (I), (Clemo, Perkin and Robinson, J.C.S., 1924, 1779) condenses readily with aromatic aldehydes to give beautifully crystalline Schiff's bases (II, R = Ph, p-MeO-C_6H_4, 3:4-$CH_2O_2C_6H_3$, o-, m-, and p-$NO_2C_6H_4$).



(I). (II).



(III) (IV). (V).

While diphenylamine-2(6')-carboxylic acids on thermal decomposition generally lose carbon dioxide to give the diphenylamine, benzylidene-2-amino-diphenylamine-6'-carboxylic acid (II, R = Ph) gives a product from which anhydro-2-amino-diphenylamine-6'-carboxylic acid (III) is the only pure substance which has been isolated. This compound is identical with that obtained by Clemo, Perkin and Robinson (loc. cit.,) by thermal decomposition of (I).

Benzylidene-2-amino-diphenylamine (IV) on thermal decomposition gives 1-anilino-acridine (V), (c.f. Reddelien's synthesis of acridine from benzylidene-aniline (Ber., 1920, 53, 356), and Ullmann and la Torre's synthesis of α- and β-naphthacridines from benzylidene α- and β-naphthylamines (Ber., 1904, 37, 2922)).

E X P E R I M E N T A L./

E X P E R I M E N T A L.

2-Amino-diphenylamine-6'-carboxylic acid (I).

2-Nitro-diphenylamine-6'-carboxylic acid (prepared as in Synthesis 7, Part III of this Thesis) (32.5g.) in a mixture of ammonia (d .880, 135c.c.) and water (135c.c.) was treated gradually in the hot with a hot solution of ferrous sulphate (315g. in 375c.c. water). The mixture was filtered hot and the residue washed with hot dilute ammonia. The filtrate treated with sulphur dioxide gave crude 2-amino-diphenylamine-6'-carboxylic acid which was crystallised from alcohol.

Benzylidene-2-amino-diphenylamine-6'-carboxylic acid (II, R = Ph).

Amine-acid (4.6g.) and benzaldehyde (2.1g.) were mixed and the solid formed crystallised from alcohol when it formed yellow needles m.p. 152° decomp. Yield 5g. (Found: N, 8.97 $C_{20}H_{16}O_2N_2$ requires N, 8.86%).

p-Methoxybenzylidene-2-amino-diphenylamine-6'-carboxylic acid (II, R = p-$MeOC_6H_4$).

Amine-acid (2.28g.) and anisaldehyde (1.36g.) treated as above gave yellow needles from alcohol m.p. 177° decomp. Yield 3.5g. (Found: N, 8.14. $C_{21}H_{18}O_3N_2$ requires N, 8.09%).

3':4'-Methylenedioxybenzylidene-2-amino-diphenylamine-6'-carboxylic acid (II, R = $CH_2O_2C_6H_3$).

Amine-acid (2.28g.) and piperonal (1.5g.) were heated together in alcohol (30c.c.) and allowed to stand to crystallise when yellow needles separated. Yield 2.7g. Crystallised from EtOH this had m.p. 171° decomp. (Found: N, 7.94. $C_{21}H_{16}O_4N_2$ requires N, 7.77%).

p-/

p-Nitrobenzylidene-2-amino-diphenylamine-6'-carboxylic acid (II, R = p-$NO_2C_6H_4$).

Amine-acid (2.28g.) dissolved in alcohol (100c.c.) and p-nitro-benzaldehyde (1.5g.) added gave in a few moments a solid which was filtered, washed and dried (3g.). Crystallised from alcohol a dark reddish solid with little crystalline structure was obtained m.p. 195° decomp. (Found: N, 11.82. $C_{20}H_{15}O_4N_3$ requires N, 11.63%).

m-Nitrobenzylidene-2-amino-diphenylamine-6'-carboxylic acid (II, R = m-$NO_2C_6H_4$).

Amine-acid (1.14g.) was dissolved in alcohol (50c.c.) and m-nitro-benzaldehyde (0.75g.) added. No precipitate formed on cooling but on addition of water the condensation compound was obtained. This was filtered, dried (1.5g.) and crystallised from alcohol gave yellow needles m.p. 188° decomp. (Found: N, 11.69. $C_{20}H_{15}O_4N_3$ requires N, 11.63%).

o-Nitrobenzylidene-2-amino-diphenylamine-6'-carboxylic acid (II, R = o-$NO_2C_6H_4$).

Amine-acid (2.28g.) dissolved in alcohol was treated with o-nitro-benzaldehyde (1.5g.) and on standing for a short time separated red squat needles which were filtered, washed and dried. This compound changes colour and decomposes at 205°. Yield 2.9g. (Found: N, 11.3. $C_{20}H_{15}O_4N_3$ requires N, 11.63%).

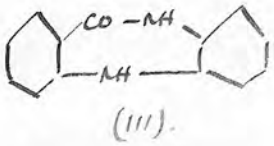
Thermal decomposition of benzylidene-2-amino-diphenylamine-6'-carboxylic acid.

Benzylidene-2-amino-diphenylamine-6'-carboxylic acid (5g.) was heated at 160° for some time and then distilled under reduced pressure when 3.5g. of a heavy oil passed over and solidified to a glass on cooling. Most of this was lost on attempting to crystallise from xylene when 0.7g. of yellowish plates/

plates separated. These crystallised again from xylene had m.p. 245°. (Note. In repetitions of this experiment attempts were made to use other solvents but always most of the distillate dissolved and could not be obtained crystalline. This is very suggestive that it contains benzylidene-2-amino-diphenylamine, see below).

Constitution of the compound m.p. 245°.

This compound was found insoluble in dilute but soluble in concentrated hydrochloric acid. The solution in concentrated sulphuric acid showed no fluorescence and on addition of potassium dichromate and diluted gave a black solid. The solution in concentrated hydrochloric acid treated with a fragment of sodium nitrite and diluted gave a purplish coloured solution and a black solid. The solution added to alkaline β-naphthol gave a faint greenish colour but no decided dye formation. This suggested absence of a primary amino group. The analysis C, 74.55; H, 4.82 (micro-combustion Schoeller); N, 13.6 suggests the molecular formula $C_{13}H_{10}ON_2$ which requires C, 74.3; H, 4.76; N, 13.3%. The constitution (III) is therefore probable.



(III).

This compound has already been prepared by Clemo, Perkin and Robinson (loc. cit.,) and when prepared by their method was found to have m.p. 248-249° (see below). Mixed m.p. test with the compound m.p. 245° showed no depression: so that the constitution (III) is the correct one for the substance isolated from the thermal decomposition of the benzylidene derivative./

derivative.

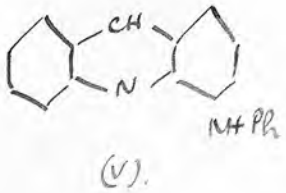
Anhydro-2-amino-diphenylamine-6'-carboxylic acid.
2-Amino-diphenylamine-6'-carboxylic acid was refluxed with xylene for several hours, the solution cooled and the solid which separated crystallised from xylene and then from aqueous pyridine when it formed brownish-yellow plates m.p. 248-249° (Clemo, Perkin and Robinson, 250°).

2-Nitro-diphenylamine. (c.f. Kehrmann and Haras, Ber., 1913 46, 341).
o-Chloro-nitrobenzene (50g.), aniline (70g.) and anhydrous sodium acetate (26g.) were heated under reflux for 12-13 hr. in an oil-bath at 215°. The product was steam-distilled to remove unchanged aniline and o-chloro-nitrobenzene; then some concentrated hydrochloric acid was added and the mixture steam-distilled again for ½ hr. On standing to cool a red oil formed in the distillation flask. This became solid on pouring off the aqueous layer and washing with water. The solid filtered, washed and crystallised from alcohol formed large flakey crystals of the required o-nitro-diphenylamine m.p. 73-75°.

2-Amino-diphenylamine. (c.f. Kehrmann and Haras, loc. cit., 342).
(Note. o-Nitro-diphenylamine cannot be reduced to the corresponding amine by West's method of reduction (J.C.S., 1925, 494) probably due to the fact that iron compounds have a profound effect on 2-amino-diphenylamine).
o-Nitro-diphenylamine (15g.) in spirit (150c.c.) was added hot to a mixture of $SnCl_2 2H_2O$ (60g.) in conc. HCl (150c.c.) and heated on the water-bath till all the nitro compound had disappeared and a green solution resulted. The alcohol was then/

then distilled off and the residue diluted with twice its volume of water and stirred when the tin double salt crystallised. This was filtered when cold, and sucked dry at the pump. The crystals were dissolved in hot alcohol, treated with excess of ammonia and filtered. The filtrate diluted largely with water gave white crystals which separated, dried and crystallised from dilute alcohol formed the desired 2-amino-diphenylamine m.p. 76-78°. Yield 8.7g.

Benzylidene-2-amino-diphenylamine and its thermal decomposition. 2-Amino-diphenylamine (7.36g.) and benzaldehyde (4.24g.) were mixed and warmed carefully till no more water was given off and the deep yellow coloured liquid became clear. On cooling, the mass gradually hardened to a glassy solid which could not be crystallised from any of the common solvents. This benzylidene compound was warmed poured into a distilling flask and distilled under reduced pressure with no apparent change. When heated to its b.p. at atmospheric pressure for some time and again completely distilled under reduced pressure a yellow oil passed over. This was dissolved in a small quantity of hot xylene and left standing overnight when colourless needle-shaped crystals separated. These were collected and crystallised from dilute alcohol in fine white needles m.p. 103°. This compound is readily soluble in benzene, but insoluble in petroleum ether. The analyses C, 84.36; H, 5.20 (micro-combustion Schoeller); N, 10.47 indicate the formula $C_{19}H_{14}N_2$ which requires C, 84.4; H, 5.2; N, 10.4% for which the constitution (V) is advanced.



(V).

The/

The compound is slightly soluble in concentrated hydrochloric acid and is not precipitated on dilution. The dilute acid solution treated with sodium nitrite and added to an alkaline solution of β-naphthol gave no decided dye formation and therefore indicates the absence of a primary amino group.

A P P E N D I X I.

List of Compounds which have been submitted to the Chemotherapy Committee of the General Medical Council for test of Anti-malarial value.

1. 1-Chloro-4-N-piperidino-acridone hydrochloride (very slightly active).
2. 1-Bromo-4-N-piperidino-acridone hydrochloride (very slightly active).
3. Sodium salt of 1-N-piperidino-acridone-3-sulphonic acid (not active).
4. 1:5-Diphenyl-3-N-piperidinoethyl-pyrazoline lactate (not active).
5. 1-N-piperidino-5-furyl-4-pentene-3-one hydrochloride (not active).
6. 1-Dimethylamino-5-furyl-4-pentene-3-one hydrochloride (not active).
7. 1-Diethylamino-5-furyl-4-pentene-3-one hydrochloride (not active).
8. 1-N-piperidino-5-(p-methoxyphenyl)-4-pentene-3-one hydrochloride (not active).
9. 1:4-Di-(β-benzoylethyl)-piperazine-dihydrochloride (not active).
10. 1-N-piperidino-3-(2-thienyl)-propan-3-one hydrochloride (not active).
11. 1-N-dimethylamino-3-(2-thienyl)-propan-3-one hydrochloride (not active).
12. 1-Phenyl-3-(N-piperidinoethyl)-5-(2-furyl)-pyrazoline hydrochloride (not active).

A P P E N D I X II.

List of Papers published by the Author.

1. "The Reduction of Nitro Compounds by Aromatic Ketols. Part 1. Some p-Azoxy-compounds".
   by H.B. Nisbet. J.C.S., 1927, 2081-2086.

2. "The Reduction of Nitro Compounds by Aromatic Ketols. Part 11. Some o-, m-, and p-Azoxy-compounds".
   by H.B. Nisbet. J.C.S., 1928, 3121-3122.

3. "Some Reactions of m-m'-Dinitrobenzil".
   by A.A. Boon and H.B. Nisbet. J.C.S., 1929, 1901-2.

4. "The Reactivity of Groups in Substituted Acridones. Part 1. The Replacement of Nitro Groups by Piperidyl and Piperazyl".
   by H.B. Nisbet and (in part) A.B. Goodlet.
   J.C.S., 1932, 2772-2773.

5. "The Reactivity of Groups in Substituted Acridones. Part 11. Cationoid Activity at Position 4 in Acridones".
   by H.B. Nisbet. J.C.S., 1933, 1372-1373.

6. "Heterocyclic Ketones. Part 1. β-Amino-ketones and Related Pyrazolines derived from Benzylidene- and Furfurylidene-acetone".
   by H.B. Nisbet and C.G. Gray. J.C.S., 1933, 839-840.